Exhibit 164
(Filed Under Seal)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-525

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA:	22-525
Proposed brand name:	Namenda XR
Generic name:	Memantine HCl
Dosage form:	Extended-Release Capsules
Dosage strengths (mg):	7, 14, 21, and 28
Indication:	Moderate to severe dementia of Alzheimer's type
Sponsor:	Forest Laboratories, Inc.
Submission type:	Original NDA (505 (b)(1))
Submission date:	August 20, 2009
OCP division:	DCP1 (HFD-860)
OND division:	Neurology products
Primary reviewer:	Huixia Zhang, PhD
Team leader:	Raman Baweja, PhD
Pharmacometrics reviewer:	Hao Zhu, PhD
Pharmacometrics Team leader:	Yaning Wang, PhD

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the data submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA22-525 and finds the data acceptable. OCP supports approval of Memantine HCl (Namenda XR) 7, 14, 21, 28 mg extended release capsules. OCP recommends that Namenda XR be taken once daily with or without food.

1.2 Phase IV Commitments

No Phase IV study recommendation.

1.3 *Summary of Clinical Pharmacology and Biopharmaceutics Findings*

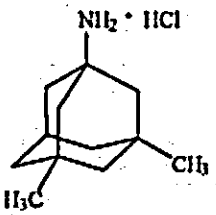
Regulatory Background

Memantine Immediate Release (IR) was approved in Germany in 1978 for organic brain syndrome (nor dementia), parkinson's disease, and spasticity. As of 2002, memantine is marketed in 23 countries for the treatment of mild to moderate dementia. Also since 2002, the European Union has allowed a sponsor (Merz) to market memantine for moderately severe to severe Alzheimer's disease. Since 2003, memantine IR has been approved in U.S. for moderate to severe Alzheimer's disease (Forest Labs.). The recommended starting dose of memantine is 5 mg once daily, and the recommended target dose is 20 mg/day as 10 mg BID. The dose should be increased in 5 mg weekly increments.

This applications was filed as a 505 (b)(1) NDA. Namenda XR, memantine hydrochloride (HCl) extended-release (ER) capsules, is submitted for the treatment of moderate to severe dementia of Alzheimer's type. Namenda XR will be marketed in four strengths (7 mg, 14 mg, 21 mg, and 28 mg) for once daily administration. The lower strengths are to be used during up-titration and for severely renally-impaired patients.

Drug Description

NAMENDA XR is an orally active N-methyl-D-aspartate (NMDA) receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:



The molecular formula is $C_{12}H_{21}N \cdot HCl$ and the molecular weight is 215.76. Memantine HCl occurs as a fine white to off-white powder and is soluble in water.

NAMENDA XR capsules are supplied for oral administration as 7, 14, 21 and 28 mg capsules. Each capsule contains extended release beads with the labeled amount of memantine HCl and the following inactive ingredients: sugar spheres, polyvinylpyrrolidone, hypromellose, talc, polyethylene glycol, ethylcellulose, ammonium hydroxide, oleic acid, and medium chain triglycerides in hard gelatin capsules.

Proposed Therapeutic Indication and Dosage Regimen

Namenda XR is indicated for the treatment of moderate to severe dementia of Alzheimer's type. The recommended initial dose of Namenda XR is 7 mg once daily, and a maintenance dose of 28 mg once daily is suggested. A minimum of 1 week of treatment with the previous dose should be observed before increasing the dose. For patients with severe renal impairment, a target dose of 14 mg once daily is recommended.

Relative Bioavailability of Namenda XR

The relative bioavailability of Namenda XR capsule to the IR tablet is 96%.

Bioequivalence between the to-be-marketed commercial capsule and the clinical trial capsule

Following single dose administration of 28 mg (highest strength) memantine ER under fasted condition, the to-be-marketed commercial, Ireland formulation and clinical Inwood formulation are bioequivalent.

Switchability from Namenda IR to Namenda XR in Patients

A patient who is stabilized with NAMENDA® IR formulation 10 mg twice daily may directly switch to the XR formulation at a dose of 28 mg once daily with no additional titration or lag time.

Similar memantine exposure can be achieved immediately after the formulation change. A comparison between the steady state memantine PK profiles using 10 mg BID dosing of IR formulation and the memantine PK profile following the first switched dose (28 mg QD) of XR formulation was made. The mean steady state concentration within 24 hours following 10 mg BID dosing of IR formulation was in a range between 88.7 and 118.8 ng/mL. Simulation indicated that memantine concentration was in a range of 94.9-105.3 ng/mL on Day 1 after the formulation switching to XR. It is clear that similar memantine exposure can be achieved on Day 1 following the formulation switching. Therefore, the efficacy, tolerability and safety profiles are expected to be similar prior to and immediately after the formulation switching.

Following long-term treatment of 28 mg QD XR formulation, the mean memantine exposure gradually increased to the range of 114.9 – 147.8 ng/mL. With higher exposure

than that achieved using 10 mg BID dosing of IR formulation, efficacy is maintained with no drastic adverse events noted.

Dose Adjustment in Severely Renal-Impaired Patients

A patient with normal renal function who is stabilized with NAMENDA ® IR formulation 10 mg twice daily may directly switch to XR formulation at a dose of 28 mg once daily with no additional titration or lag time. Further, based on IR labeling, since severely-renally impaired patients are dosed on a 5 mg twice daily regimen, which is at one half (1/2) the level of that of the patients with normal renal function, the switch from IR to XR for severely-renally impaired patients should parallel that of the normals at one half (1/2) dose level. Thus, a target dose of 14 mg/day is recommended in patients with severe renal impairment. No dosage adjustment is recommended in patients with mild or moderate renal impairment.

Drug-Drug Interaction Between Memantine and Bupropion, an antidepressant

No effect of memantine on bupropion or on CYP2B6 activity (hydroxylation of bupropion) was found, nor was there an effect of bupropion on memantine.

Food Effect on the Pharmacokinetics of Memantine ER and Sprinkling on Applesauce

Administration of 28-mg Memantine ER under fed and fasted conditions showed that exposures of memantine were comparable. However, time to peak exposure of the TBM ER capsules were significantly shorter (~7.5 hr) under fed conditions (17.6 hr) than under fasted conditions (25.1 hr). Namenda XR can be given with or without food.

Memantine ER capsule emptied onto applesauce before administration is bioequivalent to memantine ER capsule administered intact, when the highest strength of 28 mg was studied.

Ethanol Dose-Dumping Effect

For all dose strengths (7 mg, 14 mg, 21 mg, 28 mg), moderate dose-dumping effect of ethanol on memantine ER capsule was observed in 20% v/v alcohol at 2 hrs, and a pronounced effect was observed in 40% v/v ethanol as early as 30 min. The extreme situation of dose dumping with 40% alcohol for the 28 mg strength means that the entire capsule dose would be released in 30-45 minutes. Single 40 mg doses of memantine in a PK study were safe and well tolerated, and the adverse events observed were mild in intensity. Further, according to the sponsor, worldwide post marketing and clinical trials experience for doses up to 100 mg revealed that the adverse events were mild and reversible. Efficacy will not be decreased with one incidence or infrequent consumption of alcohol. Thus, there is no concern about alcohol consumption from a clinical pharmacology standpoint.

2. QUESTION BASED REVIEW (QBR)

2.1 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA.

In Vivo:

- SD, fasting, Relative BA, formulation selection study (XR vs IR, 40 mg, MEM-PK-13): an open-label, randomized, four-way crossover bioavailability study comparing memantine modified release capsules to immediate release tablet in human subjects

- SD, Bridging BA/BE, and Food effect study (To-Be-Marketed vs Clinical; 28 mg – highest strength; MEM-PK-17): a randomized, open-label, three-way crossover, single-dose bioequivalence and food-effect study of the clinical formulation and the to-be-marketed modified-release formulation of memantine HCl in healthy human subjects

- SD and MD Relative BA study (28 mg QD TBM XR vs 10 mg BID IR; MEM-PK-23): evaluation of memantine pharmacokinetics following single- and multiple-dose administration of a memantine HCl extended-release capsule and immediate-release tablet in human subjects

- MD PK study (one arm, 28 mg TBM, MEM-PK-18): a multiple-dose, open-label study evaluating the pharmacokinetics of a memantine HCl modified-release (MR) capsule at steady-state in healthy human subjects

- Sprinkled vs Intact, BE study (SD, 28 mg trade, MEM-PK-24): open-label, two-way crossover, single-dose, fasting bioequivalence study in healthy human subjects comparing intact administration of a memantine HCl extended-release capsule with administration of capsule contents sprinkled on soft food

- DDI study: Memantine IR and Bupropion (IR 30 mg SS, MRZ 90001-0519/1): a single centre, randomized, double-blinded, placebo-controlled, multiple dose, three-period one-sequence cross-over study of the pharmacokinetic interaction of 30 mg memantine on CYP2B6 with its substrate bupropion in healthy male volunteers

In Vitro:

- Alcohol dose-dumping experiment (all 4 strengths: 7-mg, 14-mg, 21-mg, 28-mg in pH1.2 NaCl/HCl medium with 5%, 20%, 40% alcohol, v/v)

Clinical/Medical Studies in Patients with Moderate to Severe Alzheimer's Disease:

- Efficacy and safety study (MEM-MD-50): a randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in patients with moderate to severe dementia of the Alzheimer's type

The efficacy measures were to assess efficacy in terms of cognitive and functional outcomes:

The instrument measuring cognition was the Severe Impairment Battery (SIB) which is a 51 item set with scores ranging from 0-100: 100 best; low score severe impairment.

The overall function was measured as Activities of Daily Living Inventory (ADL) which is 19 item set of questions with 54 points signifying optimal performance.

There were 677 patients enrolled with 1:1 randomization into two groups namely memantine ER added to a stable dose of AChE I (stabilized for at least 3 months), or placebo added to a stable dose of AChE I (stabilized for at least 3 months). Most of the patients were stabilized on donezepil, while the remaining were on either rivastigmine or galantamine.

- Safety study (MEM-MD-51): an open-label evaluation of the safety of memantine in patients with moderate to severe dementia of the Alzheimer's type

- Safety study (MEM-MD-54): an open-label extension study evaluating the safety and tolerability of memantine in patients with moderate to severe dementia of the Alzheimer's type

2.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

This application was filed as a 505(b)(1) NDA. Namenda XR (memantine ER) is submitted for the treatment of moderate to severe dementia of the Alzheimer's type, which is the same indication approved for the Immediate-Release formulation.

Namenda IR tablets in 5 mg and 10 mg strengths were approved in the US on October 16, 2003. The approved IR formulation is twice daily dosing to the target dose at 20 mg/day (10 mg BID). This twice daily dosing regimen for the IR has been by convention from previous experience of administering the drug in European countries and the US sponsor continued to maintain twice daily dosing. Simulation performed by OCP for dosing 20 mg IR of memantine once daily versus its current dosing of 10 mg IR BID indicated that the concentration time profiles were comparable between the two regimens.

A new memantine extended release formulation (bead formulation, Namenda XR) has now been developed by the same sponsor (Forest Research Institute, Inc.) to allow for prolonged release and absorption of memantine following oral administration, which

provides convenience with less frequent dosing. The target maintenance dosage of memantine ER (Namenda XR) is 28 mg once daily.

2.2.1 What is the mechanism of action and the proposed therapeutic indication for Namenda XR?

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease.

It is used to treat moderate to severe dementia of the Alzheimer's type.

2.2.2 What are the proposed dosage strengths and the route of administration?

Four strengths: 7 mg, 14 mg, 21 mg, and 28 mg are proposed for once daily oral administration. The capsules of the four strengths differ only in the amount of encapsulated beads.

2.2.3 What is the proposed dosing regimen for Namenda XR?

Dosing recommendations for memantine IR dosing were based on previous clinical experience from Europe since 1978. In initial studies, the dropout rate increased because of rapid dose escalation as for example 20-60 mg/day. It was then decided to proceed with slower upward titration, and was done by reducing incremental dose to 5 mg in weekly intervals. Therefore, dosing recommendations for IR are based on vast information available from several years of clinical experience in Europe.

The recommended starting dose of Namenda XR is 7 mg/day. The recommended target dose is 28 mg once daily. The dose should be increased in 7 mg increments to 28 mg once daily. The minimum recommended interval between dose increases is one week, and only if the previous dose has been well tolerated. The maximum recommended dose is 28 mg once daily. The once daily dosing regimen is based on patient convenience.

2.2.4 What drugs are approved in the US for the same indication?

Donepezil, Tacrine, Rivastigmine, Galantamine, Memantine (IR formulation)

2.3 General Clinical Pharmacology and Biopharmaceutics

2.3.1 Are the active moieties in the plasma (or biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moiety, memantine, which is the parent drug, has been adequately identified and measured in the plasma (refer to Section 2.4 on Analytical Methods).

2.3.2 Exposure

2.3.2.1 Are the exposure after administration of daily doses of Namenda XR and Namenda IR similar?

2.3.2.1.1 Are the exposures equivalent after single dose administration (ER vs IR)?

(A) Formulation selection study:

After a single 40 mg dose of memantine, bioequivalence between IR formulation and ER formulation was not demonstrated (MEM-PK-13). Mean C_{max} for ER formulation (Formulation II, selected for further development) was reduced by 35% compared to the IR formulation (Table 1). However, AUC values were equivalent based on the 90% confidence intervals which were within the range of 80% to 125% (Table 1). The relative bioavailability for selected formulation II was 96%.

Table 1: Pharmacokinetic Parameters (Mean ± SD) of Memantine After a Single 40 mg Oral Administration of Memantine Hydrochloride Extended- and Immediate-Release Formulations

PK Parameters	ER Formulation II (n=22)	IR Tablet (n=22)	LS Means Ratios and 90% Confidence Interval (ER/IR)
C_{max} (ng/ml)	39.15±7.93	59.83 ± 12.91	65.6 (63.00-68.38)
AUC_{0-t} (hr*ng/mL)	4352±752	4522±801	95.9 (92.18-99.78)
$AUC_{0-\infty}$ (hr*ng/mL)	4484±776	4653±830	96.1 (92.25-100.04)
T_{max} (hr)	33.0±7.7	6.1±1.3	P<0.001[a]
$T_{1/2}$ (hr)	62.7±8.0	64.1±10.4	

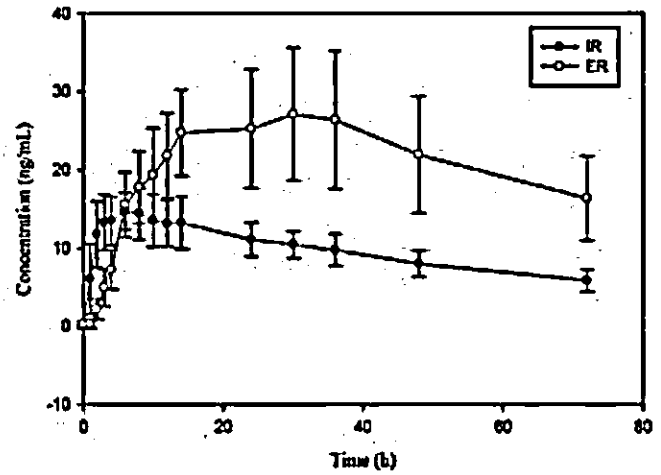
[a] p-value for T_{max}

(B) Highest strength Namenda 28 mg XR vs IR 10 mg:

Another single dose study comparing the pharmacokinetics of the selected 28-mg memantine XR capsule and a 10-mg memantine IR tablet was conducted (MEM-PK-23). Maximum plasma drug concentration (C_{max}) value for the ER formulation was 85% higher than the IR treatment. The T_{max} was significantly delayed following administration of the ER (26.1 ± 9.4 hr) than the IR formulation (5.9 ± 2.5 hr).

Table 2: Pharmacokinetic Parameters of Memantine After Single Oral Administration of either 10-mg Immediate-Release Memantine HCl Tablet or 28-mg Extended Release Memantine Capsule				
PK Parameters	28-mg ER capsule Mean±SD (n=20)	10-mg IR tablet Mean±SD (n=20)	Ratio of Geometric Means, % (ER/IR)	90% CI or p-value
C_{max}, ng/mL	29.66±7.56	16.04±3.89	-	-
C_{max}/D, ng/mL/mg	1.06±0.27	1.60±0.39	64.9	59.53-70.84
AUC_{0-72}, hr*ng/mL	1515.86±431.29	695.64±149.58	-	-
AUC_{0-72}/D, hr*ng/mL/mg	54.14±15.40	69.56±14.96	75.4	68.66-82.89
T_{max}, hr	26.11±9.39 30.0(8.0-36)[a]	5.90±2.45 6.0(2.0-10.0)[a]	-	P<0.0001
[a] Median (range)				

Figure 1. Mean (±SD) Memantine Plasma Concentrations (ng/mL) Versus Time Following A Single Oral Administration of either 10-mg Immediate-Release Tablet or 28-mg Extended-Release Capsule on Day 1



2.3.2.1.2 Are the exposures equivalent after multiple dose administration of ER formulation vs IR formulation?

(A) In study MEM-PK-23, 28-mg ER QD was compared to 10-mg IR BID, when both were dosed to steady state. Mean $C_{max,ss}$, AUC_{0-24}, and $C_{min,ss}$ of memantine at steady state following administration of memantine HCl ER capsule were 48%, 33% and 16%

greater than the corresponding values following memantine IR tablet administration (Note: all are un-normalized values). Fluctuation in the plasma levels of memantine over the steady-state dosing interval was greater for the ER (37%) compared with the IR (15%) dosing regimen. There is large variability in the data for both XR and IR. Because of the long half life of memantine, the difference in fluctuation is not clinically important. The average steady state concentration (C_{ave}) for the IR formulation was about 93 ng/mL, and for the ER formulation, it was about 127 ng/mL. The 36.5% increase in C_{ave} for the ER is comparable to the increase in dose between XR and IR (40%). AEs were mild in nature and the most common was headache. T_{max} for ER was 9.5 hrs, compared with that of IR which was 6.6 hrs.

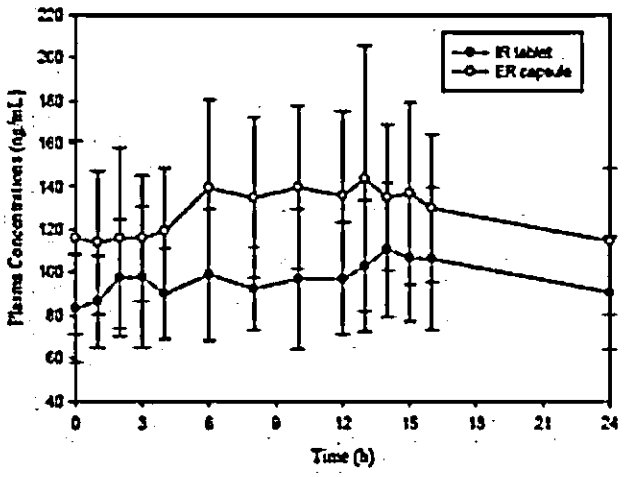
PK parameters of memantine following multiple-dose administration of the ER and IR formulations are presented in Table 3 below.

Table 3: Mean Steady-State Pharmacokinetic Parameters of Memantine on Day 29 Following Administration of either 28-mg ER Memantine HCl Capsule or 10-mg IR Memantine HCl Tablet

PK Parameters	28-mg ER Capsule, QD Mean ± SD (N = 20)	10-mg IR Tablet, BID Mean ± SD (N = 20)	Ratio of Geometric Means (%), ER/IR	90% CI or p-Value
$C_{max,ss}$, ng/mL	163.1 ± 68.2	109.2 ± 36.6	147.9	134.5-162.7
$C_{min,ss}$, ng/mL	113.5 ± 35.2	95.9 ± 27.2	116.4	104.2-130.0
C_{ave}, ng/mL	127.4 ± 34.7	93.5 ± 25.5	-	-
$AUC_{0-\tau}$, ng•h/mL	3057.9 ± 833.4	1121.5 ± 306.1	-	-
AUC_{0-24}, ng•h/mL	3057.9 ± 833.4	2324.6 ± 652.7	132.7	123.18-143.1
$T_{½}$, h	56.7 ± 8.4	58.5 ± 10.9	-	-
$T_{max,ss}$, h	9.5 ± 3.8 9.0 (6.0-16.0)[a]	6.6 ± 3.7 7.0 (2.0-11.95)[a]	-	p = 0.100
Swing	0.48 ± 0.50	0.15 ± 0.12[b]	-	-
Fluctuation	0.37 ± 0.29	0.15 ± 0.11[b]	-	-
AI	4.62 ± 1.34	7.27 ± 1.42	-	-
CL/F, L/h	8.20 ± 2.38	7.87 ± 1.83	-	-

[a] Median (range). [b] N = 17. AI = accumulation index; $AUC_{0-\tau}$ = area under the plasma concentration versus time during the dosing interval τ at steady state; C_{av} = average steady-state plasma drug concentration; CL/F = oral plasma clearance; $C_{max,ss}$ = maximum plasma drug concentration at steady state; $C_{min,ss}$ = minimum plasma drug concentration at steady state; PK = pharmacokinetic; $T_{½}$ = terminal elimination half-life; $T_{max,ss}$ = time of maximum plasma drug concentration following administration at steady state.

Figure 2. Mean (±SD) Memantine Plasma Concentrations (ng/mL) Versus Time Following Administration of either 10-mg Immediate-Release Tablet Twice Daily or 28-mg Extended-Release Capsule Once Daily at Steady State



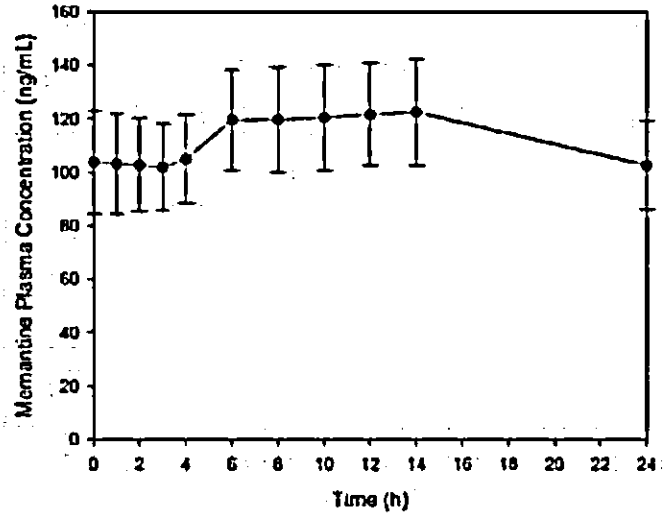
(B) The sponsor studied the pharmacokinetics of memantine ER as per its proposed labeling in another one-arm multiple dose study (MEM-PK-18: one 7-mg memantine HCl ER capsule once daily Days 1-3; one 14-mg memantine HCl ER capsule once daily Days 4-9; one 21-mg memantine HCl ER capsule once daily Days 10-15; one 28-mg memantine HCl ER Days 16-29). The steady-state pharmacokinetic parameters are presented in Table 4 below.

Table 4: Steady-State Pharmacokinetic Parameters of Memantine on day 29 following a Once-Daily Oral Administration of 28-mg Memantine ER Capsules.

PK Parameters	Mean±SD (N=18)
C_{max} (ng/ml)	127.08±21.09
C_{min} (ng/ml)	102.52±16.53
C_{ave} (ng/mL)	113.58±17.92
T_{max}, hr	11.1±2.8 12 (6.0-14.0)[a]
$T_{1/2}$, hr	55.7±9.5
$AUC_{0-\tau}$, hr*ng/mL	2726±430
Swing	0.24±0.07
Fluctuation	0.21±0.05

[a] Median (range)

Figure 3. Mean (±SD) Memantine Plasma Concentrations vs Time Over the 24-hour Dosing Interval at Steady State Following Once-Daily Administration of a 28-mg Memantine HCl Modified-Release Capsule on Day 29



A cross-study comparison of the PK parameters for memantine 28 mg ER capsules in the two multiple dose studies: MEM-PK-23 vs MEM-PK-18 indicates that most parameters are comparable, including AUC (exposure) which were within 12% of each other, and C_{max} was about 22% different. However, a large inter-individual variability for the swing and fluctuation parameters was observed in study MEM-PK-23 (Table 5).

Table 5: Comparison of Steady-State PK parameters (Mean±SD) of Memantine in Study MEM-PK-23 vs Study MEM-PK-18

PK Parameters	MEM-PK-23 (N=20)[a]	MEM-PK-18 (N=18)[a]
C_{max} (ng/ml)	163.06 ± 68.17	127.08±21.09
C_{min} (ng/ml)	113.54 ± 35.19	102.52±16.53
C_{ave} (ng/mL)	127.41 ± 34.73	113.58±17.92
T_{max}, hr	9.45 ± 3.79 9.0 (6.0-16.0)[a]	11.1±2.8 12(6.0-14.0)[a]
$T_{1/2}$, hr	56.69 ± 8.44	55.7±9.5
AUC_{0-t}, hr*ng/mL	3057.87 ± 833.39	2726±430
Swing	0.48 ± 0.50	0.24±0.07
Fluctuation	0.37 ± 0.29	0.21±0.05
[a] Median (range)		

2.3.2.2 Is the To-Be-Marketed Namenda XR product manufactured in Ireland bioequivalent to the clinical formulation manufactured at Inwood, NY?

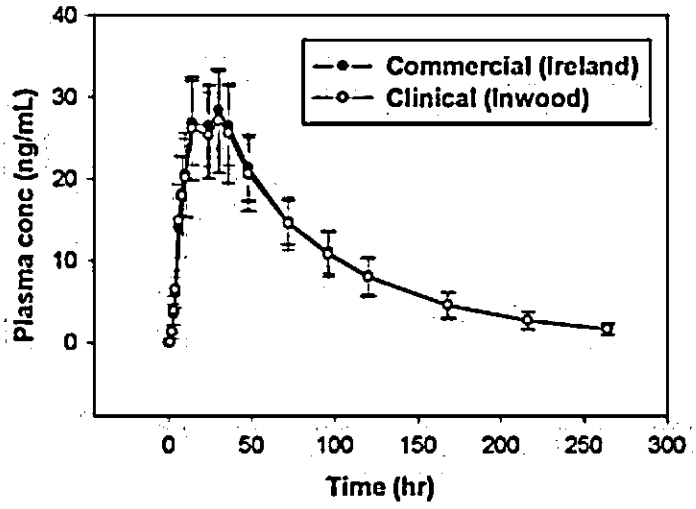
Following a single dose administration of 28 mg of memantine ER capsule, the highest strength, under fasted condition, the to-be-marketed (commercial) formulation and the clinical formulation were shown to be bioequivalent (C_{max} and AUC) based on the 90% confidence intervals which fell within the range of 80% to 125%. The T_{max} values were comparable (~ 26 hr) for the two formulations.

Table 6: Plasma Pharmacokinetic Parameters (mean±SD) for Memantine ER after a Single 28 mg Oral Administration: Commercial Formulation vs Clinical Formulation

PK Parameters	Commercial Formulation (Ireland) (n=22)	Clinical Formulation (US) (N=22)	Ratios of means,% (90%CI) Commercial/Clinical formulation
C_{max}, ng/ml	29.4±5.1	28.2±6.0	104.4 (97.4-111.9)
AUC_{0-t}, hr*ng/mL	2619.7±533.7	2562.7±595.2	101.9 (96.1-108.1)
$AUC_{0-\infty}$, hr*ng/mL	2766.6±597.2	2706.6±655.2	101.9 (96.1-108.1)
T_{max}, hr	25.1±7.4 30 (14-36)[a]	26.7±8.3 30 (14-36)[a]	1.6 (0.38)[b]
$T_{1/2}$, hr	60.3±12.3	59.8±8.9	100.8

[a] Median (range) [b] Difference of arithmetic mean (p-value)

Figure 4. Plasma Concentrations Mean (± SD) Time Profile of Memantine After a Single Dose of a 28-mg Capsule of Memantine HCl MR (Ireland, or Inwood)



2.3.2.3 Is Namenda XR bioequivalent under fed and fasted conditions?

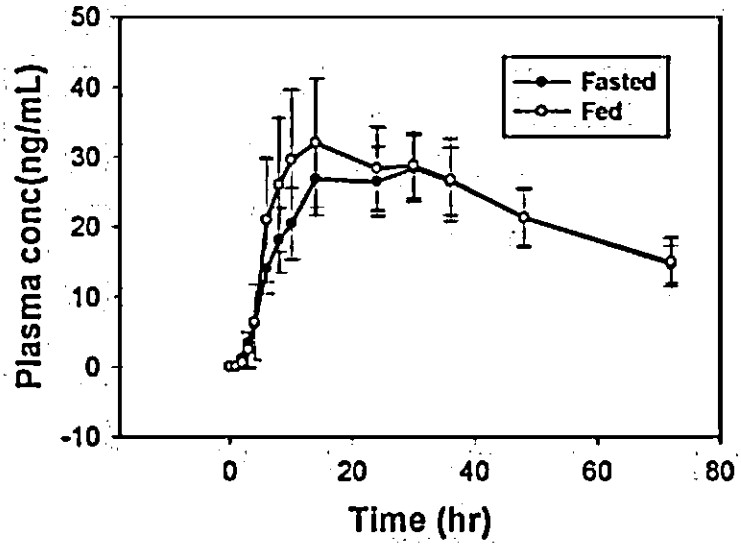
The sponsor conducted a fed study using the FDA standardized high-fat and high-calorie breakfast. Following single dose administration of 28-mg XR (to-be-marketed formulation, highest strength), memantine is bioequivalent under fed and fasted conditions. T_{max} was significantly shorter (by ~7.5 hr) under fed conditions (Table 7, Figure 5).

Table 7: Plasma Pharmacokinetic Parameters (mean±SD) for Memantine XR Under Fed vs Fasted Conditions

PK Parameters	Fed (n=22)	Fasted (n=22)	Ratios of means,% (90%CI) Fed/Fasted
C_{max}, ng/ml	33.4±8.9	29.4±5.1	111.4 (104.0-119.4)
AUC_{0-t}, hr*ng/mL	2787.9±676.3	2619.7±533.7	105.6 (99.6-112)
$AUC_{0-\infty}$, hr*ng/mL	2945.3±740.9	2766.6±597.2	105.7 (99.6-112.1)
T_{max}, hr	17.6±8.6 14 (6-36)	25.1±7.4 30 (14-36)[a]	7.5 (0.007)[b]
$T_{1/2}$, hr	60.0±9.3	60.3±12.3	99.4

[a] Median (range) [b] Difference of arithmetic mean (p-value)

Figure 5. Plasma Concentrations (Mean ±SD) Time Profiles of Memantine After a Single Dose of a 28-mg Capsule of Memantine HCl MR Under Fed or Fasted Conditions For the First 72 Hours



Based on the above results, Namenda XR can be given with or without food.

2.3.2.4 Is Namenda XR (to-be-marketed formulation) bioequivalent after sprinkling on applesauce vs an intact capsule?

Following single-dose administration of 28 mg Namenda XR in 30 healthy male and female subjects, the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (sprinkled/intact) were equivalent, suggesting that the pharmacokinetics of memantine are not altered when the contents of a capsule are emptied onto applesauce before administration.

Table 8: Pharmacokinetic Parameters (Mean ± SD) of Memantine After a Single Oral Administration of a 28-mg Memantine Extended-Release Capsule Sprinkled on a Teaspoonful of Applesauce vs Intact Capsule

PK Parameters	Sprinkled on apple sauce (n = 29)	Intact capsule (n = 29)	Ratio of Geometric Means (%), Sprinkled/Intact	90% CI or p-Value
C_{max}, ng/mL	32.7± 7.2	31.9 ± 6.3	102.1	97.1-107.2
AUC_{0-t}, ng•h/mL	2930.8 ± 517.4	2949.1± 528.9	99.4	96.2-102.7
$AUC_{0-\infty}$, ng•h/mL	3264.2 ± 624.1	3267.2 ± 661.1	100	96.6-103.5
$T_{½}$, h	61.9 ± 11.8	58.7 ± 12.7	-	-
T_{max}, h	26.6 ± 7.7 30.0 (14.0-36.2)[a]	27.5 ± 8.0 30.0 (14.0-48.0)[a]	-	p = 0.704

[a]Median (range).

2.3.2.5 What is the switchability from Namenda IR to Namenda XR in patients and is the proposed switching dosing regimen justified?

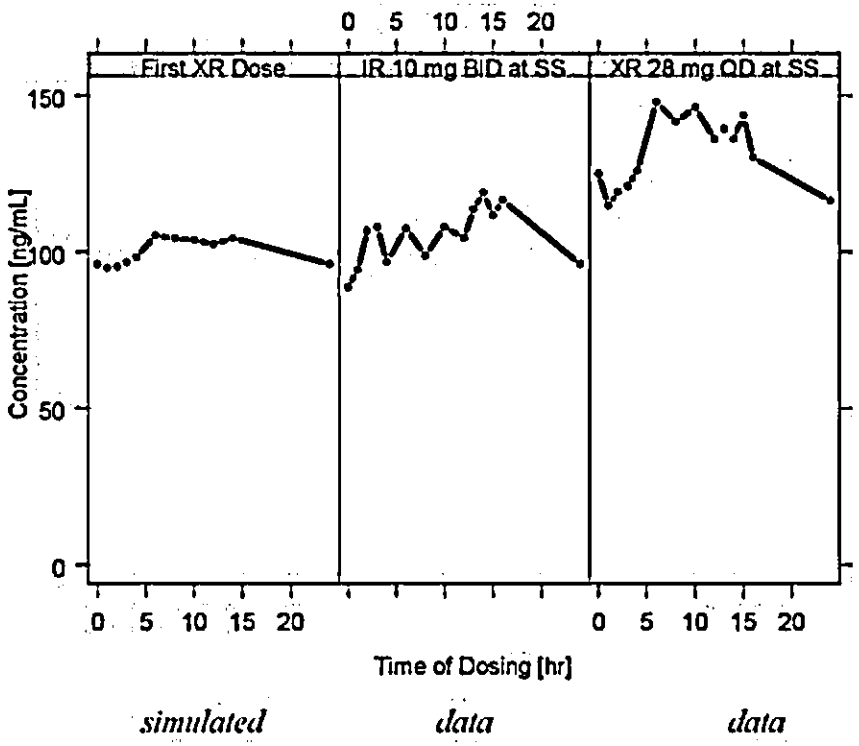
Following the sponsor's proposal, a patient who is stabilized with NAMENDA ® IR formulation 10 mg twice daily may directly switch to the XR formulation at a dose of 28 mg once daily with no additional titration or lag time.

Similar memantine exposure can be achieved immediately after the formulation change. A comparison between the steady state memantine PK profiles using 10 mg BID dosing of the IR formulation and the memantine PK profile following the first switched dose (28 mg QD) of the XR formulation was made. As shown in Figure 6, the mean steady state concentration within 24 hours following10 mg BID dosing of IR formulation was in a range between 88.7 and 118.8 ng/mL. Simulation indicated that memantine concentration was in a range of 94.9-105.3 ng/mL on Day 1 after the formulation switching to XR. This was done by superimposing the residual concentration from the IR formulation with the concentration of the first dose of 28 mg XR formulation. It is clear that similar memantine exposure can be achieved on Day 1 following the formulation switching. Therefore, the efficacy, tolerability and safety profiles were expected to be similar prior to and immediately after the formulation switching.

Following long-term treatment of 28 mg QD XR formulation, the mean memantine exposure gradually increased to the range of 114.9 – 147.8 ng/mL (based on Day 29 data). With higher exposure than that achieved using 10 mg BID dosing of IR formulation, efficacy was expected to be achieved/maintained with no drastic adverse events noted.

Short-term and long-term safety profile following the treatment of 28 mg QD formulation was further evaluated in a dedicated phase III clinical trial (Study MEM-MD-51). In Study MEM-MD-51, a total of 36 patients who were receiving memantine IR 10 mg twice daily for at least 30 days before screening were switched to memantine ER 28 mg daily. Among them, 19.4% discontinued the trial. The incidence of therapeutic emerging adverse events (TEAE) for this group of patient was 91.7% with the incidence of severe adverse events (SAE) of 27.8%. The incidences were similar between the patients who switched formulations and patients who initiated with the XR formulation.

Figure 6. Mean Memantine PK Profiles Following IR and XR Formulations



Note:

IR 10 mg BID at SS = Steady state memantine concentration following 10 mg BID dosing of IR formulation

First XR Dose = Memantine concentration following the first dose of 28 mg XR formulation in patients who were stabilized using 10 mg BID IR formulation

XR 28 mg QD at SS = Steady state memantine concentration following 28 mg QD dosing of XR formulation

2.3.2.6 Are memantine IR and ER products going to be marketed simultaneously?

Yes. Patients treated with Namenda IR tablets may be switched to Namenda XR capsules as follow:

It is recommended that a patient who is on a regimen of 10 mg twice daily of Namenda tablets be switched to Namenda XR 28 mg once daily capsules the day following the last dose of a 10 mg Namenda tablet.

2.3.2.7 Would dose adjustment of Namenda XR be needed in renally-impaired patients?

No study was conducted in the renally impaired patients in this submission.

A patient with normal renal function who is stabilized with NAMENDA ® IR formulation 10 mg twice daily may directly switch to XR formulation at a dose of 28 mg once daily with no additional titration or lag time. Further, based on IR labeling, since severely-renally impaired patients are dosed on a 5 mg twice daily regimen, which is at one half (1/2) the level of that of the patients with normal renal function, the switch from IR to XR for severely-renally impaired patients should parallel that of the normals at the half (1/2) dose level. Thus, a target dose of 14 mg/day is recommended in patients with severe renal impairment. No dosage adjustment is recommended in patients with mild or moderate renal impairment.

2.3.2.8 Does Memantine affect CYP2B6 activity in vivo and is There a Drug-Interaction Observed Between Memantine IR and Bupropion?

The rationale for investigating the inhibitory effect of memantine on CYP2B6 was based on an in vitro study that showed memantine has a Ki value of 0.51 uM in CYP2B6 supersomes; the maximal concentration at steady state for memantine following 10 mg BID dosing was 0.5 uM, thus an [I]/Ki value of 1 was obtained. Based on the Guidance, there is a high likelihood of drug interaction in vivo, and so the sponsor pursued an in vivo study.

Most patients with Alzheimer's disease also have depression. The sponsor studied the possibility of a drug-drug interaction between Memantine IR and the antidepressant, bupropion. Further they also looked at the effect of memantine on CYP2B6 activity, i.e., the conversion of bupropion to hydroxybupropion.

This was a randomized, double-blinded, placebo-controlled, multiple dose, three-period one-sequence cross-over study in 16 healthy male volunteers.

Randomized volunteers received a single 100 mg dose of bupropion in Period 1 on Day 1. In Period 2, multiple doses of memantine (up-titration to 30 mg, steady state) or placebo were administered for 22 days and continued for further 4 days in Period 3. In Period 3 Day 1, another single dose of bupropion (100 mg) was administered concomitantly with multiple dose treatment of memantine or placebo.

(A) Effect of memantine on bupropion

Bupropion:

Point estimates [90% CIs] of the ratios of $AUC_{0-\infty}$ and C_{max} of bupropion for the treatment contrast memantine+bupropion vs. bupropion were 107.6 (99.8-116.0) and 104.0 (91.5-118.2), respectively.

Table 9: Pharmacokinetic Parameters (Geometric Mean and CV (%)) of Bupropion in Period 3 (Bup +Mem) vs Period 1 (bupropion alone)

Parameters	Period 3 (Bup+Mem)	Period 1 (Bup alone)	Ratio of geometric means,% (90% CI) Bup+Mem/Bup alone
C_{max} (ng/mL)	127.16 (26.8%)	122.9 (32.3%)	104.0 (91.5-118.2)
AUC_{0-tz} (hr*ng/mL)	646.7 (15.4%)	599.3 (18.3%)	-
$AUC_{0-\infty}$ (hr*ng/mL)	658.4 (15.5%)	612.0 (18%)	107.6 (99.8-116)
T_{max} (hr)	1.0	1.0	

Median for T_{max}, mean ± SD for $T_{1/2}$; Bup: bupropion, Mem: memantine,

Hydroxybupropion:

Point estimates [90% CIs] of the ratios of $AUC_{0-\infty}$ and C_{max} of hydroxybupropion for the treatment contrast memantine+bupropion vs. bupropion were 100.7 (91.1-111.2) and 103.0 (95.8-110.6), respectively.

Table 10: Pharmacokinetic Parameters (Geometric Mean and CV (%)) of Hydroxybupropion in Period 3 (Bup +Mem) vs Period 1 (bupropion alone)

Parameters	Period 3 (Bup+Mem)	Period 1 (Bup alone)	Ratio of geometric means,% (90% CI) Bup+Mem/Bup alone
C_{max} (ng/mL)	272.98 (29.1%)	265.08 (25.6%)	103.0 (95.8-110.6)
AUC_{0-tz} (hr*ng/mL)	9225.6 (31.9%)	9071.1 (33%)	-
$AUC_{0-\infty}$ (hr*ng/mL)	9777.5 (33.3%)	9713.7 (36.5%)	100.7 (91.1-111.2)
T_{max} (hr)	4.0	3.0	-
$T_{1/2}$ (hr)	23.1±3.97	23.7±6.01	-

Median for T_{max}, mean ± SD for $T_{1/2}$; Bup: bupropion, Mem: memantine,

Overall, memantine does not affect the pharmacokinetics of bupropion.

(B) Effect of memantine on CYP2B6 activity (conversion of bupropion to hydroxybupropion)

Steady state memantine did not alter CYP2B6 activity, as reflected by the point estimates (90% CI) of the ratios of $AUC_{0-\infty}$ and C_{max} of hydroxybupropion over bupropion for the treatment contrast memantine +bupropion vs bupropion alone: 93.5 (85.6-102.1) for $AUC_{0-\infty}$, and 98.3 (89.2-108.3) for C_{max}.

Table 11: Treatment Contrasts for the Ratio of Hydroxybupropion/Bupropion	
Parameters	(Memantine + Bupropion) vs Bupropion
Ratio of $AUC_{0-\infty}$ (%)	93.5 (85.6,102.1)
Ratio of C_{max} (%)	98.3 (89.2,108.3)

(C) Effect of bupropion on memantine

After single dose administration of bupropion, the pharmacokinetics of memantine at steady state was not altered, as indicated by the point estimates of the ratios of $AUC_{0-\tau}$ and $C_{max,ss}$ of memantine in period 3 (bupropion + memantine) vs period 2 (memantine alone).

Table 12: Pharmacokinetic parameters (geometric mean and CV (%)) of Memantine in Period 3 (bupropion+memantine) vs Period 2 (memantine alone)			
Parameter	Period 3 (bupropion+memantine)	Period 2 (memantine)	Ratio of geometric means,% (90% CI) Bup+Mem/Mem alone
$C_{max,ss}$ (ng/mL)	142.16 (17.9%)	140.03 (18.7%)	101.5 (95.2,108.2)
$C_{min,ss}$ (ng/mL))	90.84 (32.4%)	88.42 (31.6%)	-
$AUC_{0-\tau}$ (hr*ng/mL)	1474.5 (18.5%)	1399.5 (20.6%)	105.4 (100.9,110.0)
$T_{max,ss}$ (hr)	3.5	5.5	-
CL_{ss}/f (mL/min)	143.1±28.34	151.3±33.06	-
Median for T_{max}, and mean ± SD for CL_{ss}/f			

Overall Conclusion:

No effect of memantine on bupropion or on CYP2B6 activity (hydroxylation of bupropion) was found, nor was there an effect of bupropion on memantine.

2.3.2.9 What are the overall adverse events profile in Phase I studies reported by the sponsor?

The sponsor reported that memantine ER was generally well tolerated. In the Phase I studies, the sponsor reported that the most common adverse events reported for memantine ER were: dizziness, headache, and nausea. Most adverse events were mild in intensity. The incidence rate in single-dose studies was about 20%, while in multiple-dose studies, the rate was increased to about 60%. The sponsor reported the most common TEAE (>4%) in Phase II studies were headache, urinary tract infection, diarrhea, dizziness, influenza, agitation, and insomnia.

2.3.2.10 What is the Quantitative and Qualitative Composition of Namenda XR formulation?

The following table (Table 13) provides the quantitative and qualitative composition of Namenda XR Extended-Release beads in both commercial and clinical formulations.

Table 13: Memantine Hydrochloride Extended-Release Beads: Formulation Compositions for the Commercial Product and Clinical Batches

	Clinical study	*MEM-PK-17 MEM-PK-18 MEM-PK-23*	*MEM-PK-17 MEM-MD-50 MEM-MD-51 MEM-MD-54*
	Manufacturing site	*Forest, Ireland*	*Forest, Inwood*
	Bead formulation		(b) (4)
	Formulation type	*Commercial*	*Clinical*
Process	*Ingredients*	*Theoretical Wt, mg/g*	*Theoretical Wt, mg/g*
Drug layering	Sugar spheres, NF (b) (4)		(b) (4)
	Memantine HCl (b) (4)		
	Talc, USP/NF		
			(b) (4)
Total (memantine HCl ER beads)			(b) (4)

a Milligrams of memantine HCl per gram of extended-release beads.
b (b) (4) is removed during the manufacturing process.
ER = extended release; HCl = hydrochloride; NA = not applicable; NF = National Formulary; USP = United States Pharmacopeia; Wt = weight.

2.3.2.11 Does ethanol in vitro have a dose-dumping effect on Namenda XR?

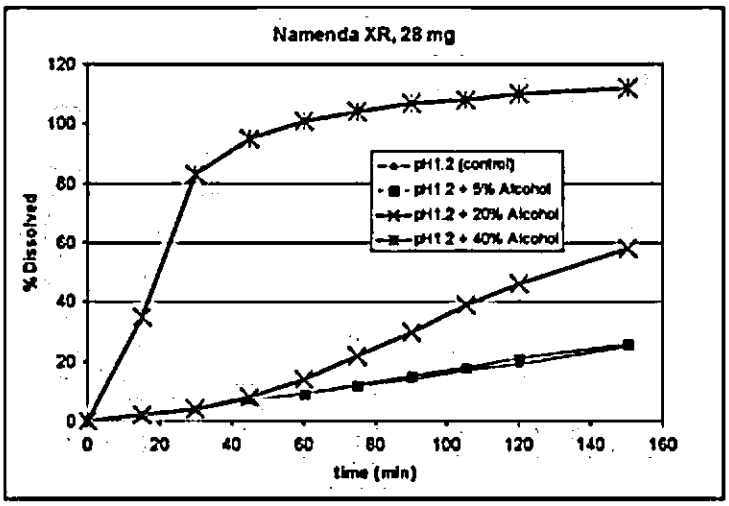
The dissolution procedure used in this experiment was similar to that used in the regular dissolution testing (USP 1 [basket], 100 rpm, 900 mL pH1.2 NaCl/HCl buffer), except that alcohol was present with various concentrations in this particular experiment.

The dissolution profiles for all 4 strengths (28-mg, 21-mg, 14-mg, 7-mg) of Namenda XR capsules are very similar. Using the 28-mg strength as the basis, no dose dumping was observed with 5% alcohol relative to the control. Minimal dose dumping occurred with 20 % alcohol, with a mean of 14% of the capsule dissolved at one hour (the control was 9%), but dose dumping has occurred at 2 hr with 46% dissolved (the control was 19%). In tests using 40% alcohol, dose dumping was more pronounced, with a mean of 95% of the capsule dissolved at 45 minutes (the control was 7%). These results indicate that nearly the entire capsule dose of 28 mg would be released in 30-45 minutes in a 40% alcohol environment.

Table 14: Dissolution Results of Memantine HCl (28-mg Strength) in pH1.2 Medium With Different Percentage of Alcohol (%)

Time (min)	0%	5%	20%	40%
0	0	0	0	0
15	2	2	2	35
30	4	4	4	83
45	7	7	8	95
60	9	9	14	101
75	12	12	22	104
90	14	15	30	107
105	17	18	39	108
120	19	21	46	110
150	25	26	58	112

Figure 7. Dissolution Profile of 28-mg Namenda XR in pH1.2 Media in the Presence of Various Concentrations of Alcohol



Moderate dose-dumping effect of ethanol on memantine ER capsule was observed in 20% v/v alcohol, and pronounced effect was observed in 40% v/v ethanol, for all dose strengths.

The extreme situation of dose dumping with 40% alcohol means that the entire capsule dose of 28 mg would be released in 30-45 minutes, i.e., ER behaving as an IR. Single 40 mg doses of memantine in a PK study were safe and well tolerated, and the AEs observed were mild in intensity. In order to understand the impact of a patient receiving a bolus of memantine 28 mg, the sponsor has looked at the adverse events for memantine in worldwide post marketing and clinical trials experience for doses up to 100 mg. The majority of the events included dizziness, somnolence, confusion, vertigo, weakness and vomiting. There were no deaths in overdoses up to 100 mg. Further, data from clinical trials for other indications where the daily dose was over 20 mg, reaching up to 100 mg, revealed the same events as mentioned above, and were mild in intensity, and were reversible. Overall, the events were mild and reversible. Efficacy will not be decreased with one incidence or infrequent consumption of alcohol. Thus, there is no concern about alcohol consumption from a clinical pharmacology standpoint.

2.4 Analytical Methods

2.4.1 What bioanalytical methods are used to assess concentrations?

Quantification of memantine and the internal standard [redacted] in human plasma was achieved using LC-MS/MS [redacted] in all but one in vivo studies submitted in this application. The exception is that in the drug interaction study, quantification of memantine was done using GC-MS (refer to individual study report 4.1.6 Drug Interaction Study section ASSAY). The calibration range for [redacted] was 0.5-100 ng/mL. The between-run and within-run imprecision (CV) and accuracy (% Norm) for three memantine QC levels of 1.5 ng/mL, 20 ng/mL, and 80 ng/mL were <10%, and <9%.

Overall, the LC-MS/MS method ([redacted]) for the quantitation of memantine met the requirements for specificity, sensitivity, accuracy, and precision. The assay method was adequately validated and is acceptable.

2.4.2 For all moieties measured, is free, bound, or total measured?

Only one moiety-memantine, the parent drug, was monitored in plasma, and total drug concentration was obtained.

2.4.3 What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques were used?

The calibration range was 0.5-100 ng/mL. For plasma concentrations that were below Lower Limit of Quantification, they were treated as zero for pharmacokinetic analysis. Linear regression was applied for all standard curves with a weighting factor of 1/concentration^2 ($1/x^2$). The correlation coefficient for memantine was 0.99 or greater.

2.4.4 What is the lower limit of quantitation? What is the accuracy, precision, and selectivity at this limit?

The lower limit of quantification in human plasma was 0.5 ng/mL, with mean accuracy and precision of –12.8% and 16.3%, respectively. No interference from human blank plasma was observed.

2.4.5 What is the sample stability under conditions used in the study?

QC samples containing memantine at three concentrations (1.5 ng/mL, 20 ng/mL, and 80 ng/mL) were stable after three freeze-thaw cycles following storage at –30°C. The mean concentrations found were within ± 5.6% of the nominal concentrations.

Memantine in the final extract was stable for approximately 4 days when stored at ambient temperature and for 7 days when stored at 4°C. Reinjection stability was established at 13 hours.

Additionally, when stored at –30°C in plasma containing sodium heparin or potassium EDTA as anticoagulant, memantine was stable for at least 516 days and at least 319 days, respectively. Memantine was stable in human plasma for at least 319 days when stored at –70°C.

For all the studies conducted, these stability data cover the period during which each study was conducted.

2.4.6 What is the recovery of memantine plasma samples?

Recovery was evaluated at three levels of memantine plasma concentrations. The recovery percentages were 73% at 5 ng/mL, 78% at 50 ng/mL, and 76% at 85 ng/mL. Overall, the assay is adequately validated.

SIGNATURES

Huixia Zhang, Ph.D.
Reviewer, Psychiatry Drug Products, DCP1
Office of Clinical Pharmacology

RD/FT initialed by Raman Baweja, Ph.D.
Team Leader, Psychiatry Drug Products, DCP1
Office of Clinical Pharmacology

Cc: NDA22-525, DCP1 (Mehta, Uppoor, Baweja, Zhang)

OCP Required Inter-Division Briefing was on April 28, 2010.

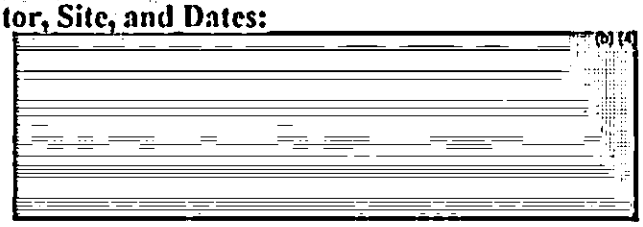
3. APPENDIX

3.1 Individual Study Reports

3.1.1 Single-Dose, Relative Bioavailability, Formulation Selection Study

An Open-Label, Randomized, Four-Way Crossover, Bioavailability Study Comparing Memantine Modified Release Capsules (Administered As a Single 40 mg Dose) to Immediate Release Tablet (2x20mg) in Human Subjects under fasting conditions.

Study Investigator, Site, and Dates:



Analytical Site and Dates:
Forest Research Institute
12/14/2004-01/07/2005

Study Number: MEM-PK-13

OBJECTIVES

To compare the bioavailability of three memantine modified release (MR) capsules to an immediate release (IR) tablet.

FORMULATIONS

Table 1. Products used in MEM-PK-13

	Manufacturer	Formulation	Lot #	Manufacture Date (Dates of Study)
Memantine HCl (IR):	Forest Laboratories, Inc.	20mg Tablet	03111K	10/2003
Memantine HCl (MR) Formulation I:	Forest Laboratories, Inc.	40mg Capsule	BN 0000042	07/2004
Memantine HCl (MR) Formulation II:	Forest Laboratories, Inc.	40mg Capsule	BN 0000053	07/2004
Memantine HCl (MR) Formulation III:	Forest Laboratories, Inc.	40mg Capsule	BN 0000055	07/2004

MR Formulation I (Treatment B) consisted of a mixture of [redacted] beads with a ratio of Release 1/Release 3 of [redacted] MR Formulation II (Treatment C) consisted of a mixture of [redacted] beads with a ratio of Release 1/Release 3 of [redacted] MR Formulation III (Treatment D) consisted of [redacted] beads.

The dissolution profiles of the IR tablet and MR capsules can be found in the Table 2 below. IR formulation tablets completely dissolved in pH1.2 medium within 30 min. For the MR capsule II, which was chosen for further development, the % dissolved in the pH1.2 medium was about [redacted] by 8 hours.

Table 2. Dissolution Profiles of Memantine IR and MR Formulations

[redacted]

STUDY DESIGN

This Study was a randomized, single center, single dose, four-way, crossover study.

A single dose of 40 mg was chosen because higher doses are required for the treatment of neuropathic pain.

Total 24 subjects were enrolled and 22 of them have completed the study. On four occasions separated by 21 days, subjects received one of the four treatments in a randomized order:

Treatment A: Single oral dose of memantine 2 x 20 mg tablets (IR) given at 0800 hours
Treatment B: Single oral dose of memantine 40 mg capsule (MR) Formulation I
Treatment C: Single oral dose of memantine 40 mg capsule (MR) Formulation II
Treatment D: Single oral dose of memantine 40 mg capsule (MR) Formulation III

Dosing was done at 0800 hours on Days 1, 22, 43, and 64 for all subjects.

Blood samples for determination of memantine concentrations in plasma were collected by a qualified phlebotomist using a pre-chilled 5 mL Vacutainer tube (containing tri-potassium EDTA as an anticoagulant) on Days 1, 22, 43, 64 at 0 (pre-dose), 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, 11, 12, 14, 24, 36, 48, 72, 96, 144, 192, 240, 288 and 336 hours post dose. After [redacted]

ASSAY

Memantine and its internal standard [redacted] were extracted and quantified following a validated LC/MS/MS [redacted] This [redacted] was validated to demonstrate the accuracy, linearity, reproducibility, and precision of the analytical procedure. The assay was linear in the concentration range of 0.5-100 ng/mL. Using 0.5 mL of plasma, the limits of quantification for memantine for this assay ranged from 0.5 ng/mL (lower limit of quantification, LLOQ) to 100 ng/mL (upper limit of quantification, ULOQ).

Excluding 5 outliers (not within 15% acceptance criteria; 2 at 0.5 ng/mL, 1 at 1 ng/mL, 2 at 2 ng/mL) from the 225 standard samples, the precision and accuracy of memantine standards that were run for this study samples were within 5.1% and 1.1%, respectively. The performance of this method during the sample analysis is summarized below.

Table 3. Performance of the analytical [redacted] for plasma samples from study MEM-PK-13

	Quality Control Samples		
	1.5 ng/mL	20 ng/mL	80 ng/mL
Accuracy (% bias)	-0.7	-2.0	0.5
Precision (% CV)	4.7	2.4	2.3

Eighteen (18) samples among 2197 samples from this study were reassayed. For 14 out of the 18 samples (77.8%), the reassay value fell within 20% variation of the respective original values.

Memantine plasma samples (with EDTA present) were found to be stable for 319 days at -30 °C and -70°C. Also it was demonstrated to be stable after 3 freeze/thaw cycles. For this particular study, the study period was from 09/09/2004-12/14/2004, and the sample was analyzed between 12/14/2004 and 01/07/2005. From the time the first sample that was collected till the time the last sample was analyzed, the period lasted for about 4 months. Therefore, these stability data cover the period during which the study was conducted.

Overall, the assay is adequately validated.

SAFETY ASSESSMENT

Blood pressure and pulse rate were measured in the sitting position (subjects were sitting for at least 5 minutes), on the same arm throughout the study and before any

corresponding blood sample was collected. In addition to the pre- and post-study measurements, vital signs were taken at the following times:

On Days 1, 22, 43 and 64: Pre-dose, 2, 4, 6, 8 and 24 hours after the 0800 hour dose administration.

Subjects who had a systolic blood pressure greater than 140 mmHg or less than or equal to 90 mmHg, or a diastolic blood pressure greater than or equal to 90 mmHg or less than or equal to 50 mmHg had their blood pressure reassessed until the abnormal value fell within range or judged not clinically significant by the Investigator. Subjects who had a pulse rate of greater than 100 bpm or less than 50 bpm by palpation had pulse rate reassessed until the abnormal value fell within range or judged not clinically significant by the Investigator.

RESULTS

Demographics

A total of 24 subjects were enrolled and 22 subjects completed the study.

Table 4. Demographics of Subjects Enrolled in the Study (n=24)

Mean Age (Range)	Gender (n, %)	Mean Weight (kg) (Range)	Race (n,%)
27.2±6.31 (19-42)	Male : 17 (70.8) Female: 7 (29.2)	69.3±10.44 (45-86)	Black: 6 (25%) White: 18 (75%)

Pharmacokinetics

The principle pharmacokinetic parameters describing the pharmacokinetics of memantine were derived from plasma concentrations using non-compartmental analysis with the software program WinNonlin. The sponsor claimed that plasma concentrations that were below the limit of quantification were treated as zero for all pharmacokinetic analysis. Actual sampling times were used for PK analysis.

The PK analysis population comprised of the subjects (n=22) who completed the study with evaluable PK parameters.

Figure 1 Mean (±SD) memantine plasma concentrations (ng/mL) time profile following single oral doses of 40 mg memantine HCl on a linear scale (n=22)

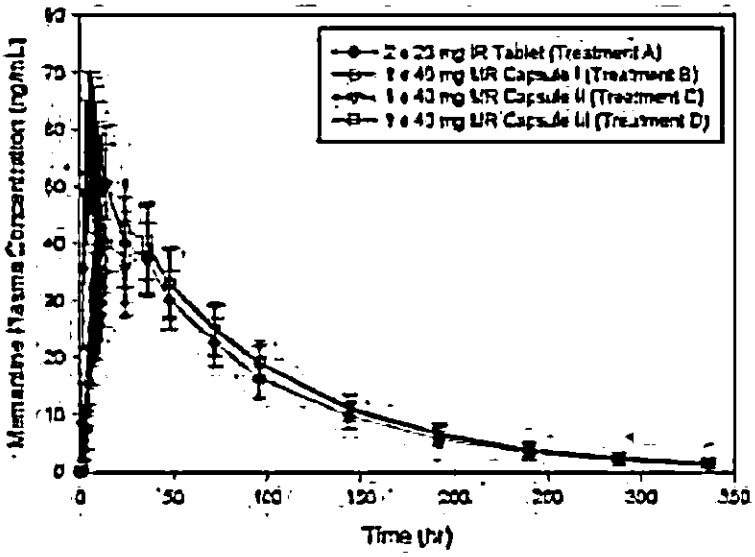
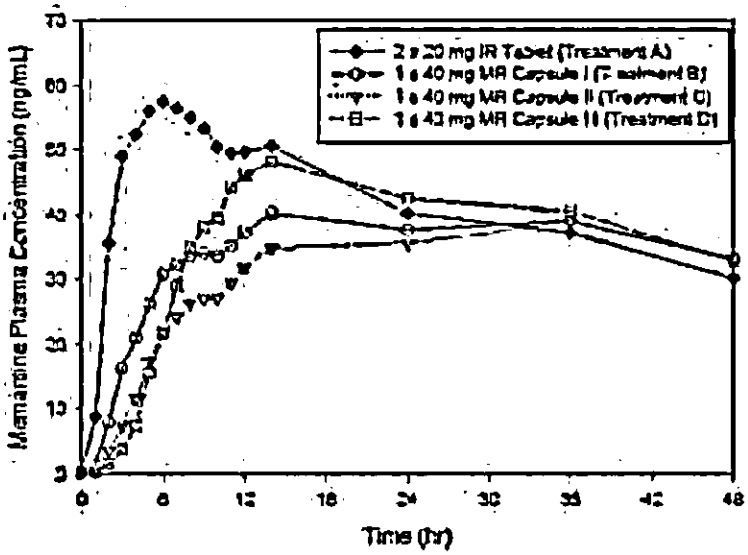


Figure 2 Mean memantine concentration (ng/mL) time profile following single doses of 40 mg memantine HCl from 0-48 hour (n=22)



Compared to Treatment A (IR tablet), the mean C_{max} values were reduced by 30.6%, 34.6%, and 17.6% following Treatments B, C, and D, respectively. AUC values showed that all formulations provided equivalent systemic exposure based on the 90% confidence intervals which were within the range of 80% to 125%. The terminal half-life of all

formulations was essentially the same. Treatments B, C and D showed an increase in the time of maximum plasma concentration (T_{max}) following the single dose administration of modified release formulations, indicating delayed release of memantine compared to Treatment A (IR tablet).

Table 5. Mean ± SD Pharmacokinetic Parameters of Memantine

PK Parameters	Treatment (A) (n=22)	Treatment (B) (n=22)	Treatment (C) (n=22)	Treatment (D) (n=22)
C_{max} (ng/ml)	59.83 ± 12.91	41.54±8.08	39.15±7.93	49.30±9.26
AUC_{0-t} (hr*ng/mL)	4522±801	4478±689	4352±752	4657±788
$AUC_{0-\infty}$ (hr*ng/mL)	4653±830	4514±710	4484±776	4826±839
T_{max} (hr)	6.1±1.3	22.0±11.2	33.0±7.7	13.7±2.6
$T_{1/2}$ (hr)	64.1±10.4	63.6±10.1	62.7±8.0	67.6±13.8

LS Means Ratios and 90% Confidence Interval (CI)						
	Treatment B vs Treatment A		Treatment C vs Treatment A		Treatment D vs Treatment A	
PK parameters	LSMeans ratio (%)[a]	90% CI or p-value[b]	LSMeans ratio (%)[a]	90% CI or p-value[b]	LSMeans ratio (%)[a]	90% CI or p-value[b]
C_{max} (ng/ml)	69.8	67.03-72.72	65.6	63.00-68.38	82.9	79.58-86.38
AUC_{0-t} (hr*ng/mL)	99.3	95.43-103.30	95.9	92.18-99.78	102.9	98.88-107.40
$AUC_{0-\infty}$ (hr*ng/mL)	99.5	95.51-103.57	96.1	92.25-100.04	103.6	99.46-107.86
T_{max} (hr)	361	<0.001	541	<0.001	225	<0.001

[a]Ratio of arithmetic means for Tmax(%); [b]p-value for Tmax

Safety

Single 40 mg doses of memantine were safe and well tolerated. No serious adverse events were reported in the study. The most frequent adverse events reported were dizziness, headache, nausea, and paresthesia. Most adverse events were mild in intensity. Only one adverse event was severe in intensity but was not related to study drug. No subject withdrew because of an adverse event.

Of the total number of adverse events observed, 39% were observed in Treatment A, 21% in Treatment B, 18% in Treatment C, and 22% in Treatment D.

CONCLUSION

Memantine IR and ER formulations have demonstrated comparable exposure (AUC), though C_{max} was decreased, and T_{max} was delayed significantly. MR formulation II (Treatment C) was selected for further development as it had the lowest mean C_{max}, and it did not affect AUC, and was associated with the least incidence of adverse events, which probably is related to the slower release, and subsequently slower absorption of memantine, and/or the lower C_{max} levels observed with the MR formulations.

Reviewers' Comments:

OCP agrees with sponsor's conclusion that the exposure to memantine was similar between the IR and MR formulations, and Formulation II was a reasonable choice for further development.

3.1.2 Single-Dose, Bioequivalence and Food-Effect Study

A Randomized, Open-Label, Three-Way Crossover, Single-dose Bioequivalence and Food-Effect Study of the Clinical Formulation and the To-Be-Marketed Modified-Release Formulation of Memantine HCl in Healthy Human Subjects

Study Investigator, Site, and Dates:

Analytical Site and Dates:
Forest Research Institute
08/01/2007-09/21/2007

Study Number: MEM-PK-17

OBJECTIVES

1. To evaluate the bioequivalence of the memantine modified-release (MR) clinical formulation (MR I, Inwood) and the to-be-marketed MR capsule formulation (MR II, Ireland)

2. To evaluate the effect of food on the bioavailability of the memantine to-be-marketed MR capsule formulation (MR II, Ireland)

FORMULATIONS

Table 1. Products used in MEM-PK-17

	Manufacturer	Formulation	Lot #	Manufacture Date
Memantine HCl MR capsule (MR I, Inwood)	Forest Laboratories, Inc.	28 mg Capsule	BN 0001692	12/2005
Memantine HCl MR capsule (MR II, Ireland)	Forest Laboratories, Inc.	28 mg Capsule	BN 0001965	10/2006

STUDY DESIGN

This was a single-center, randomized, open-label, three-way crossover, single-dose study in 24 healthy male and female subjects 18 to 45 years of age.

A 28-mg dose of memantine, the highest strength of the drug product that is intended to be marketed, was tested in this study.

Subjects were randomized to receive each of the following three treatments separated by a 21-day washout period:

Treatment A: Single oral dose of one 28-mg capsule of memantine HCl MR (MR I, Inwood) under fasted conditions.
Treatment B: Single oral dose of one to-be-marketed 28-mg capsule of memantine HCl MR (MR II, Ireland) under fasted conditions
Treatment C: Single oral dose of one to-be-marketed 28-mg capsule of memantine HCl MR (MR II, Ireland) under fed conditions

To determine memantine plasma concentrations, blood sampling will be performed at the following times before and after the dosings on Days 1, 22, and 43:0.0 hour (predose) and 1, 2, 3, 4, 6, 8, 10, 14, 24, 30, 36, 48, 72, 96, 120, 168, 216, and 264 hours postdose.

All vacutainer and plasma tubes were prechilled in an ice bath before use.

ASSAY

Memantine and its internal standard [redacted] were extracted and quantified following a validated LC/MS/MS [redacted] The assay was linear in the concentration range of 0.5 to 100 ng/mL. With 0.5 mL of plasma, the limits of quantification for memantine in this assay ranged from 0.5 ng/mL (lower limit of quantification) to 100 ng/mL (upper limit of quantification) with sodium heparin as anti-coagulant in human plasma.

During the study, the precision and accuracy of memantine standards were within 5.7% and ± 6.0%, respectively. The precision and accuracy of memantine quality control samples were within 7.3% and ± 1.5%, respectively. The performance of the method used in the sample analysis is summarized in Table below. Overall, the assay is validated.

Table 2. Performance of the analytical [redacted] for plasma samples from study MEM-PK-17

	Quality Control Samples		
	1.5 ng/mL	20 ng/mL	80 ng/mL
Accuracy (% bias)	0.7	-1.5	-0.8
Precision (% CV)	7.3	4.1	3.6

Memantine plasma samples (with EDTA present) were found to be stable for 319 days at -30°C and -70°C. Also it was demonstrated to be stable after 3 freeze/thaw cycles. For this particular study, the study period was from 05/10/2007-07/02/2007, and the sample analysis date was from 08/01/2007 to 09/21/2007. From the time the first sample that was collected till the time the last sample was analyzed, the period lasted for about 4 months, shorter than the stable storage time of 319 days. Therefore, these stability data cover the period during which the study was conducted.

Out of the 1348 samples that were collected for this study, only 3 samples were reassayed. Two (2) of the 3 samples passed the reassay twice (difference within 20% of the original value), and one (1) of the 3 samples only passed the reassay once.

SAFETY ASSESSMENT

BP and pulse rate were measured with the subject in the sitting position (subjects were sitting for at least 5 minutes) on the same arm throughout the study and before any corresponding blood samples were collected. In addition to the Screening and End-of-Study visits, BP and pulse rate were measured at the following times:

Days 1, 22, 43: 0.0 hour (predose) and 3, 6, and 12 hours after the 0800-hours dose administration
Days 2, 23, 44: 24, 30, and 36 hours after the 0800-hours dose administration on the previous day
Days 3, 24, 45: 48 hours after the 0800-hours dose administration on Days 1, 22, and 43

Additional vital signs were assessed as deemed necessary by the PI. The BP of subjects who had an abnormal systolic BP (≥ 140 mm Hg or ≤ 90 mm Hg) or abnormal diastolic BP (≥ 90 mm Hg or ≤ 50 mm Hg) was to be reassessed until the abnormal value fell within range or was judged by the PI to be not clinically significant. The pulse rate of subjects who had a pulse rate of greater than 100 bpm or less than 50 bpm by palpation was to be reassessed until it fell within range or was judged by the PI to be not clinically significant. If on reassessment, BP and/or pulse rate remained at values the PI considered to be clinically significant, the subject was to be dropped from the study.

RESULTS

Demographics

Table 3. Demographics of Healthy Subjects Enrolled in the Study (n=24)

Age (Range)	Gender (n, %)	Weight (kg) (Range)	Race (n,%)	Ethnicity (n,%)
34.5±8.7 (19-45)	Male: 14 (58.3) Female: 10 (41.7)	69.47±11.57 (45.5-91.8)	Black: 3 (12.5) White: 21 (87.5)	Hispanic (22, 91.7) Non-Hispanic (2, 8.3)

Twenty-four (24) subjects were enrolled in the study, and 23 completed it. For PK analysis, only 22 subjects were analyzed because of the vomiting from one subject.

Safety

No serious AEs or deaths occurred during the study, and no subjects were discontinued because of an AE. Fifteen (15) TEAEs were reported by 8 subjects. Most of the events were mild in severity and possibly related to study drug. The most common TEAEs (≥ 3 TEAEs) were headache (6 TEAEs reported by 4 subjects) and dizziness (4 TEAEs reported by 3 subjects).

Overall, the single oral administration of 28-mg memantine HCl MR capsules was safe and well tolerated in healthy subjects.

Pharmacokinetics

The principle pharmacokinetic parameters describing the pharmacokinetics of memantine were derived from plasma concentrations using non-compartmental analysis with the software program WinNonlin. The sponsor claimed that plasma concentrations that were below the limit of quantification were treated as zero for all pharmacokinetic calculations. Actual sampling times were used for PK analysis.

The PK analysis population comprised of all subjects (n=23) who completed the study with evaluable PK parameters, however, one subject was excluded from the data analysis because of vomiting (n=22).

(A) Bioequivalence between To-Be-Marketed Ireland capsule vs Clinical Inwood capsule

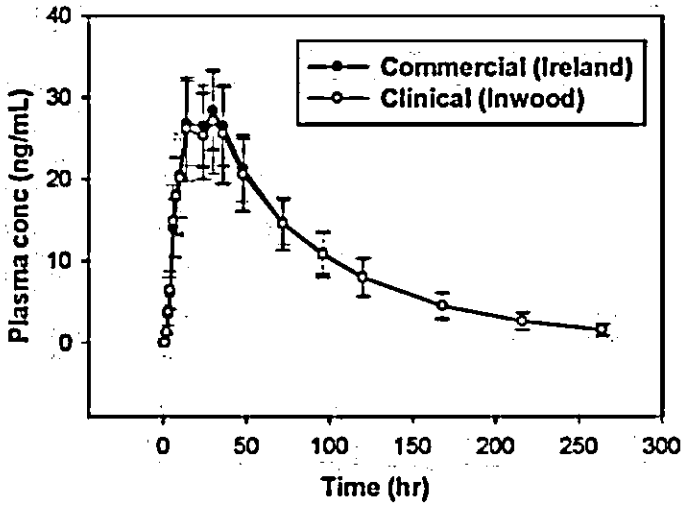
Following single dose administration of 28 mg (the highest strength) Namenda XR under fasted condition, the to-be-marketed (commercial) formulation and the clinical formulation were shown to be bioequivalent (both C_{max} and AUC), based on the 90% confidence intervals which fell within the range of 80% to 125%. T_{max} values were comparable (~26 hr).

Table 4: Plasma Pharmacokinetic Parameters (mean±SD) for Memantine ER after a Single 28 mg Oral Administration: Commercial Formulation vs Clinical Formulation

PK Parameter	Commercial Formulation (Ireland) (n=22)[a]	Clinical Formulation (Inwood, US) (N=22)[a]	Ratios of means,% (90%CI)[b] Commercial/Clinical formulation
C_{max}, ng/mL	29.4±5.1	28.2±6.0	104.4 (97.4-111.9)
AUC_{0-t}, hr*ng/mL	2619.7±533.7	2562.7±595.2	101.9 (96.1-108.1)
$AUC_{0-\infty}$, hr*ng/mL	2766.6±597.2	2706.6±655.2	101.9 (96.1-108.1)
T_{max}, hr	25.1±7.4 30 (14-36)[c]	26.7±8.3 30 (14-36)[c]	1.6 (0.38)[d]
$T_{1/2}$, hr	60.3±12.3	59.8±8.9	100.8

[a] One subject was excluded from analysis because of vomiting.
[b] Data presented are percentage ratios of the geometric mean (90% CI) for AUC and C_{max}, arithmetic means for $T_{1/2}$, and difference-of-arithmetic means for T_{max}. The 90% CI of log-transformed AUC and the 90% CI of C_{max} were based on an analysis-of-variance model with sequence, subject nested within sequence, treatment, and period as factors.
[c] Median (range).
[d] p-value of Wilcoxon signed rank test between the test and the reference.

Figure 1. Plasma Concentrations Mean (± SD) Time Profiles of Memantine After a Single Dose of a 28-mg Capsule of Memantine HCl MR (Inwood, or Ireland)



(B) Food-Effect on To-Be-Marketed commercial formulation (Ireland)

The sponsor conducted a fed study using the FDA standardized high-fat and high-calorie breakfast. Food has no effect on the exposure to memantine. The 90% CIs of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the commercial formulation under fed conditions versus fasted conditions fell within the bioequivalence range of 80% to 125. Tmax was shorter by ~ 7.5 hrs under fed conditions. Elimination half-life was similar (≈ 60 hours) under both conditions.

Table 5: Plasma Pharmacokinetic Parameters (mean±SD) for Memantine XR Under Fed vs Fasted Conditions

PK Parameter	Fed (n=22)	Fasted (n=22)	Ratios of means,% (90%CI)[b] Fed/Fasted
C_{max}, ng/ml	33.4±8.9	29.4±5.1	111.4 (104.0-119.4)
AUC_{0-t}, hr*ng/mL	2787.9±676.3	2619.7±533.7	105.6 (99.6-112)
$AUC_{0-\infty}$, hr*ng/mL	2945.3±740.9	2766.6±597.2	105.7 (99.6-112.1)
T_{max}, hr	17.6±8.6 14 (6-36)	25.1±7.4 30 (14-36)[a]	7.5 (0.007)[d]
$T_{1/2}$, hr	60.0±9.3	60.3±12.3	99.4

[a] One subject was excluded from analysis because of vomiting.
[b] Data presented are percentage ratios of the geometric mean (90% CI) for AUC and C_{max}, arithmetic means for $T_{1/2}$, and difference-of-arithmetic means for T_{max}. The 90% CI of log-transformed AUC and the 90% CI of C_{max} were based on an analysis-of-variance model with sequence, subject nested within sequence, treatment, and period as factors.
[c] Median (range).
[d] p-value of Wilcoxon signed rank test between the test and the reference.

Figure 2. Plasma Concentrations Mean (± SD) Time Profiles of Memantine After a Single Dose of a 28-mg Capsule of Memantine HCl MR Under Fed or Fasted Conditions

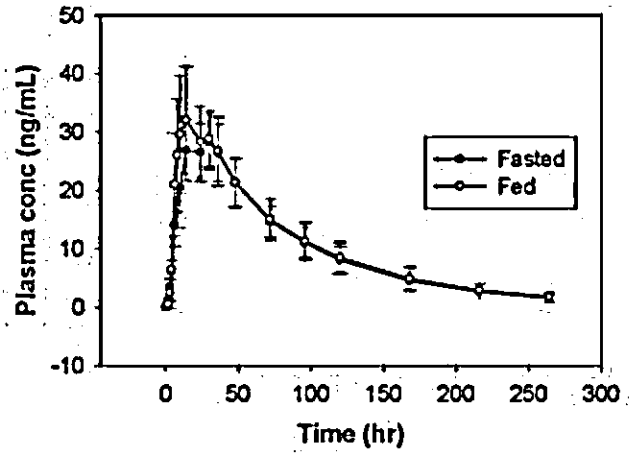
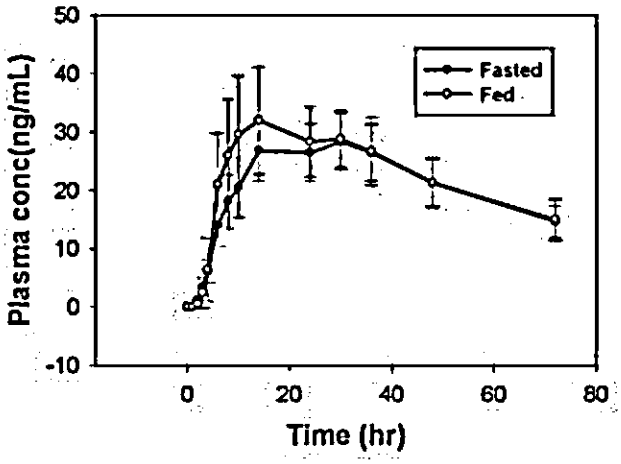


Figure 3. Plasma Concentrations (Mean ±SD) Time Profiles of Memantine After a Single Dose of a 28-mg Capsule of Memantine HCl MR Under Fed or Fasted Conditions For the First 72 Hours



CONCLUSIONS

Memantine was safe and well tolerated after a single oral administration of a 28-mg memantine HCl MR capsule in healthy subjects.

The memantine MR clinical formulation (Inwood) and the to-be-marketed memantine MR capsule formulation (Ireland) were bioequivalent.

Food had no statistically significant effect on the oral bioavailability of the to-be-marketed MR capsule formulation (Ireland). Time to peak exposure of the to-be-marketed MR capsule formulation (Ireland) was significantly shorter by 8 hrs under fed conditions (17 hr) than under fasted conditions (25 hr).

Reviewers' comments

OCP agrees with the sponsor that the to-be-marketed formulation (Ireland) showed bioequivalence to the clinical formulation (Inwood).

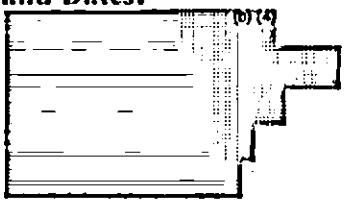
OCP agrees that food does not have a statistical significant effect on the extent of absorption of the MR memantine, though Tmax was shorter by ~ 7.5 hrs under fed conditions. Therefore, the to-be-marketed commercial formulation can be taken regardless of food.

However, considering the significant role (bridging between clinical formulation and To-Be-Marketed formulation) this study plays, an inspection was requested.

3.1.3 Single- and Multiple-Dose Relative Bioavailability Study

Evaluation of Memantine Pharmacokinetics Following Single- and Multiple-Dose Administration of a Memantine HCl-Extended-Release Capsule and Immediate-Release Tablet in Healthy Human Subjects

Study Investigator, Site and Dates:



Analytical Site and Dates:

Forest Research Institute
8/12/2008-10/1/2008

Study Number: MEM-PK-23

OBJECTIVES

1. To evaluate the pharmacokinetics of memantine at steady state following multiple doses of 28-mg memantine extended-release (ER) capsule once daily and 10-mg memantine immediate-release (IR) tablet twice a day (BID).

2. To evaluate the pharmacokinetics of memantine following single-dose administration of 28-mg ER capsule and 10-mg IR tablet.

FORMULATIONS

Table 1. Products used in MEM-PK-23

	Manufacturer	Formulation	Lot #	Manufacture Date
Memantine HCl 5-mg IR tablet	Forest Laboratories, Inc.	5 mg Tablet	L0002415	9/2007
Memantine HCl 10-mg IR tablet	Forest Laboratories, Inc.	10 mg Tablet	L0002410	1/2008
Memantine HCl 14-mg trade ER capsule	Forest Laboratories, Inc.	14 mg Capsule	L0001977	10/2006
Memantine HCl 21-mg trade ER capsule	Forest Laboratories, Inc.	21 mg Capsule	L0001975	10/2006
Memantine HCl 28-mg trade ER capsule	Forest Laboratories, Inc.	28 mg Capsule	L0001965	10/2006

STUDY DESIGN

This was a single-center, single-treatment, open-label, crossover, multiple-dose study.

The dosage chosen for this study, 10-mg BID for the IR tablet represents the approved dosage regimen of IR Namenda, and the 28-mg once daily dosing regimen was evaluated for efficacy and safety in patients with moderate to severe Alzheimer's disease.

A total of 26 subjects were randomized to receive the following treatments separated by a 21-day washout period:

Treatment A

Day 1: Single 10-mg IR tablet under fasted conditions
Days 4-9: 5-mg IR tablet BID
Days 10-15: 10-mg IR tablet in the morning and 5 mg IR tablet in the evening
Days 16-28: 10-mg IR tablet BID
Day 29: 10-mg IR tablet BID (morning dose under fasted conditions)

Treatment B

Day 1: Single 28-mg ER capsule under fasted conditions
Days 4-9: 14-mg ER capsule once daily
Days 10-15: 21-mg ER capsule once daily
Days 16-28: 28-mg ER capsule once daily
Day 29: 28-mg ER capsule under fasted conditions

Safety was assessed throughout the study by the monitoring of adverse events (AEs), electrocardiograms (ECGs), vital sign assessments, physical examination, and laboratory evaluations.

Blood samples were obtained at the following times to determine memantine plasma concentrations:
Days 1 and 51: 0.0 hour (predose) and 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, and 72 hours (postdose)
Days 27, 28, 77, and 78: 0.0 hour (predose)
Days 29 and 79: 0.0 hour (predose) and 1, 2, 3, 4, 6, 8, 10, 12, 13, 14, 15, 16, 24, 48, 72, 96, 144, and 192 hours (postdose)

ASSAY

Plasma concentrations of memantine were measured using LC-MS/MS following [redacted] The assay was linear in the concentration range of 0.5 to 100 ng/mL. Using 0.5 mL of plasma, the limits of quantification for memantine for this assay ranged from 0.5 ng/mL (lower limit of quantification) to 100 ng/mL (upper limit of quantification).

During the study, the precision and accuracy of memantine standards were within 6.1% and ± 2.0%, respectively. The precision and accuracy of memantine quality control samples were within 7.0% and ± 3.6%, respectively. The performance of the method during the sample analysis is summarized in the Table below.

Table 2. Performance of the analytical [redacted] for plasma samples from study MEM-PK-23.

Analyte	*Test*	*Plasma Quality Control Samples*		
		1.5 ng/mL	*20 ng/mL*	*80 ng/mL*
Memantine (including outliers)	Accuracy (% Bias)	4.7	3.6	-1.2
	Precision (% CV)	21.7	4.3	8.3
Memantine (excluding outliers)	Accuracy (% Bias)	1.6	NA	-0.3
	Precision (% CV)	7.0	NA	4.5

Memantine plasma samples (with EDTA present) were found to be stable for 319 days at -30°C and -70°C. Also it was demonstrated to be stable after 3 freeze/thaw cycles. For this particular study, the study period was from 05/03/2008-08/04/2008, and the plasma samples were analyzed from 08/12/2008 to 10/01/2008. From the time the first sample that was collected till the time the last sample was analyzed, the period lasted for about 5 months. Therefore, these stability data cover the period during which the study was conducted.

Twelve (12) samples among 1576 plasma samples from this study were reassayed. For 10 out the 12 samples (83.3%), the 1st reassay value fell within 20% variation of the original value. However, for the 2nd reassay, only 4 out of the 12 samples (33.3%), their reassayed values fell within 20% variation of the original values.

SAFETY ASSESSMENT

Safety parameters (AEs, ECG parameters, vital signs, physical examination, and clinical laboratory evaluations) were summarized for all subjects who took at least one dose of study drug. Incidence tables are presented for AEs and are categorized by severity and relationship to study drug.

Any AE occurring subsequent to the first dose of study drug, regardless of the relationship to study drug, was counted as a treatment-emergent adverse event (TEAE), whether it was not present at baseline or if it was present at baseline but increased in severity during the treatment period. For other safety parameters, descriptive statistics were calculated. Subjects with potentially clinically significant (PCS) postbaseline safety values on ECG parameters, vital signs, and/or clinical laboratory parameters are listed.

RESULTS

Demographics

Table 3. Demographics of Healthy Subjects Enrolled in the Study (n=26)

Age (Range)	Gender (n, %)	Weight (kg) (Range)	Race (n,%)	Ethnicity (n,%)
27.8±6.79 (19-44)	Male: 15 (57.7) Female: 11 (42.3)	71.82±11.08 (52.9-95.8)	Black: 6 (23.1) White: 17 (65.4) Asian: 1 (3.8) Other: 2 (7.7)	Hispanic: 10 (38.5%) Non-Hispanic 16 (61.5%)

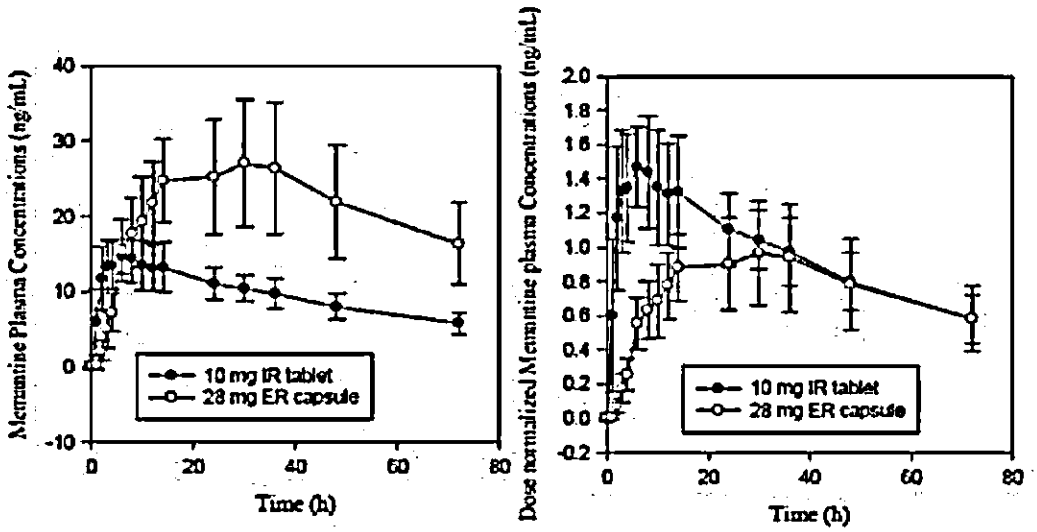
A total of 26 subjects were randomized in the study and received at least one dose of study medication, and 20 completed the study. For PK analysis, only 20 subjects were analyzed.

Pharmacokinetics

(A) Single Dose

This single dose study comparing the pharmacokinetics of the selected 28-mg memantine XR capsule and a 10-mg memantine IR tablet was conducted. Maximum plasma drug concentration (C_{max}) value for the ER formulation was 85% higher than the IR treatment. The T_{max} was significantly longer following administration of the ER (26.1 ± 9.4 hours) than with the IR formulation (5.9 ± 2.5 hours).

Figure 1. Mean (±SD) Memantine Plasma Concentrations (ng/mL) Versus Time Following a Single-Dose Administration of 10-mg Immediate-Release Tablet and 28-mg Extended-Release Capsule



A summary of the single-dose PK parameters of memantine following administration of a single 10-mg IR tablet or a single 28-mg ER capsule is presented below:

Table 4. Pharmacokinetic Parameters of Memantine After Single Oral Administration of either 10-mg Immediate-Release (Treatment A) Memantine HCl Tablet or 28-mg Extended Release (Treatment B) Memantine Capsule

PK parameter	28-mg ER capsule Mean±SD (n=20)	10-mg IR tablet Mean±SD (n=20)	Ratio of Geometric Means, % ER/IR	90% CI or p-value
C_{max}, ng/mL	29.66±7.56	16.04±3.89	-	-
C_{max}/D, ng/mL/mg	1.06±0.27	1.60±0.39	64.9	59.53-70.84
AUC_{0-72}, hr*ng/mL	1515.86±431.29	695.64±149.58	-	-
AUC_{0-72}/D, hr*ng/mL/mg	54.14±15.40	69.56±14.96	75.4	68.66-82.89
T_{max}, hr	26.11±9.39 30.0(8.0-36)[a]	5.90±2.45 6.0(2.0-10.0)[a]	-	P<0.0001

[a] Median (range)
AUC_{0-72} = area under the plasma concentration versus time curve from time zero to 72 hours; AUC_{0-72}/D = dose-normalized AUC_{0-72}; C_{max} = maximum plasma drug concentration; Cm_{ax}/D = dose-normalized C_{max}; ER = extended release; IR = immediate release; T_{max} = time of maximum plasma drug concentration.

(B) Steady State

Mean $C_{max,ss}$, AUC_{0-24}, and $C_{min,ss}$ of memantine at steady state following administration of memantine HCl ER capsule were 163 ng/mL, 3058 ng•h/mL, and 114 ng/mL, respectively, and were 48%, 33% and 16% greater than the corresponding values following administration of the memantine IR tablet. The rate of memantine absorption at steady state following once-daily administration of memantine HCl ER capsule was slower (T_{max} of 9.5 hours) compared with that following twice-daily administration of memantine IR tablet (T_{max} of 6.6 hours).

Fluctuation in the plasma levels of memantine over the steady-state dosing interval was greater for the ER (37%) compared with the IR (15%) dosing regimen. Because of the large variability of the data, and the long half life of memantine, the difference in fluctuation is not clinically important. The average steady state concentration (C_{ave}) for the IR formulation was about 93 ng/mL, and for the ER formulation, it was about 127 ng/mL. The 36.5% increase in C_{ave} for the ER is comparable to the increase in dose

(40%). Elimination half-life averaged 58.5 hours (range, 43-83 hours) and 56.7 hours (range, 47-75 hours) for the IR tablet and ER capsule, respectively.

Figure 2. Mean (±SD) Memantine Plasma Concentrations (ng/mL) Versus Time Following Administration of either 10-mg Immediate-Release Tablet Twice Daily or 28-mg Extended-Release Capsule Once Daily on Day 29 (A) or at Steady State (B)

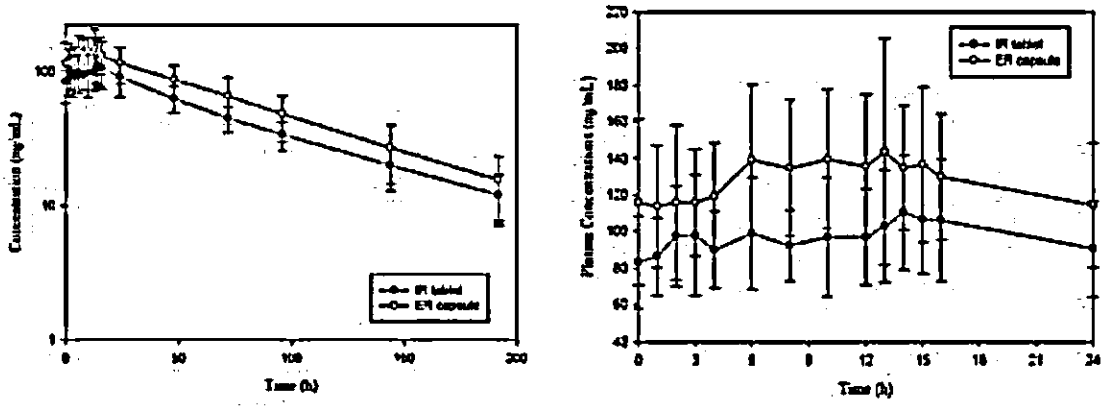
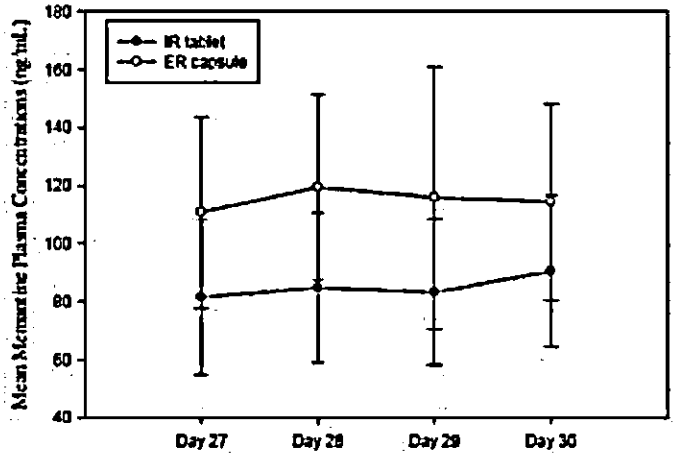


Figure 3. Mean (±SD) Memantine Plasma Concentrations (ng/mL) Before Dosing on Days 27, 28, 29, and 24 Hours Post-Day 29 Dosing



A summary of the steady-state PK parameters of memantine following a once-daily administration of 28 mg memantine HCl ER capsule and IR tablet is presented in the table below.

Table 5. Mean Steady-State Pharmacokinetic Parameters of Memantine on Day 29 Following Administration of either 28-mg ER Memantine HCl Capsule or 10-mg IR Memantine HCl Tablet

PK parameters	*28-mg ER Capsule, Mean ± SD (N = 20)*	*10-mg IR Tablet, Mean ± SD (N = 20)*	*Ratio of Geometric Means, %, ER/IR*	*90% CI or p-Value*
$C_{max,ss}$, ng/mL	163.06 ± 68.17	109.19 ± 36.62	147.9	134.51-162.66
$C_{min,ss}$, ng/mL	113.54 ± 35.19	95.90 ± 27.19	116.4	104.23-130.01
C_{av}, ng/mL	127.41 ± 34.73	93.46 ± 25.50	-	-
$AUC_{0-\tau}$, ng•h/mL	3057.87 ± 833.39	1121.47 ± 306.06	-	-
AUC_{0-24}, ng•h/mL	3057.87 ± 833.39	2324.62 ± 652.68	132.7	123.08-143.13
T½, h	56.69 ± 8.44	58.47 ± 10.88	-	-
$T_{max,ss}$, h	9.45 ± 3.79 9.0 (6.0-16.0) [a]	6.59 ± 3.71 7.0 (2.0-11.95) [a]	-	p = 0.100
Swing	0.48 ± 0.50	0.15 ± 0.12 [b]	-	-
Fluctuation	0.37 ± 0.29	0.15 ± 0.11 [b]	-	-
AI	4.62 ± 1.34	7.27 ± 1.42	-	-
CL/F, L/h	8.20 ± 2.38	7.87 ± 1.83	-	-

[a] Median (range). [b] N = 17.
AI = accumulation index; $AUC_{0-\tau}$ = area under the plasma concentration versus time during the dosing interval τ at steady state; C_{av} = average steady-state plasma drug concentration; CL/F = oral plasma clearance; $C_{max,ss}$ = maximum plasma drug concentration at steady state; $C_{min,ss}$ = minimum plasma drug concentration at steady state; $T_{½}$ = terminal elimination half-life; $T_{max,ss}$ = time of maximum plasma drug concentration following administration at steady state.

Safety

There were no serious adverse events (SAEs) or deaths observed in the study. Overall, 51 treatment-emergent adverse events (TEAEs) were reported by 19 subjects during the course of the study. All TEAEs were mild in severity, and approximately half of the incidents were possibly related to study drug.

The most common TEAEs were headache, back pain, dizziness, and viral upper respiratory tract infection with incidence rates of 34.6%, 19.2%, 19.2%, and 11.5%, respectively.

CONCLUSIONS

Overall, once-daily administration of 28-mg memantine HCl ER capsule and twice-daily administration of 10-mg memantine HCl IR tablet were safe and well tolerated. There were no deaths or SAEs in this study.

Following single-dose administration, the dose-normalized C_{max} was 35% lower for the ER capsule than for that of the IR tablet, confirming the ER characteristics of the ER capsule. The T_{max} from the ER formulation was ~ 26 hr, vs IR formulation ~ 6 hr. ,

At steady state, elimination half-life of memantine following administration of the ER capsule (56.7 hours) was similar to that of the IR tablet (58.5 hours). Fluctuation was higher for the once-daily administration of the ER capsule than for the twice-daily administration of the IR tablet, averaging 37% for the ER dosage regimen and 15% for the IR dosage regimen.

Reviewers' Comments:

Because of the design of the study, single-dose pharmacokinetics of memantine ER was not well characterized (terminal half life 60 hrs, and blood samples only collected up to 72 hrs), therefore, a cross-study comparison could not be performed to other single-dose studies submitted in this application .

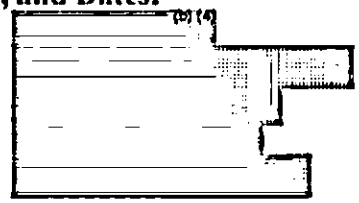
For steady-state pharmacokinetics, OCP agrees with the sponsor that multiple-dose pharmacokinetics of memantine ER is well characterized in healthy subjects. Mean $C_{max,ss}$, AUC_{0-24}, and $C_{min,ss}$ of memantine at steady state following administration of 28-mg memantine HCl ER capsule QD were 48%, 33% and 16% greater than the corresponding values following administration of memantine 10-mg IR tablet BID.

Comparing to single dose administration of memantine ER capsule, a higher incidence rate of adverse events was observed in multiple dose administration (~60% vs. ~20%).

3.1.4 Multiple-Dose, One-Arm Pharmacokinetic Study

A Multiple-Dose, Open-Label Study Evaluating the Pharmacokinetics of a Memantine HCl Modified-Release (MR) Capsule at Steady-State in Healthy Human Subjects

Study Investigator, Site, and Dates:



Analytical Site and Dates:

Forest Research Institute
10/01/2007-10/19/2007

Study Number: MEM-PK-18

OBJECTIVE

To evaluate the steady-state pharmacokinetics of memantine following administration of a modified-release (MR) capsule formulation of memantine HCl in human subjects

FORMULATIONS

Table 1. Products used in MEM-PK-18

	Manufacturer	Formulation	Lot #	Manufacture Date
Memantine HCl 7-mg trade ER capsule	Forest Laboratories, Inc.	7 mg Capsule	L0001968	10/2006
Memantine HCl 14-mg trade ER capsule	Forest Laboratories, Inc.	14 mg Capsule	L0001977	10/2006
Memantine HCl 21-mg trade ER capsule	Forest Laboratories, Inc.	21 mg Capsule	L0001975	10/2006
Memantine HCl 28-mg trade ER capsule	Forest Laboratories, Inc.	28 mg Capsule	L0001965	10/2006

STUDY DESIGN

This was a single-center, single-treatment, open-label, multiple dose study where the sponsor studied the pharmacokinetics of memantine ER as per its proposed labeling.

Memantine was titrated to 28 mg/day in increments of 7 mg to resemble the dosing regimen that was used in the phase III trial with memantine ER capsule in patients with moderate to severe Alzheimer's disease.

A total of 24 subjects received the following dosing regimen:

Days 1 through 3: one 7-mg memantine HCl MR capsule once daily
Days 4 through 9: one 14-mg memantine HCl MR capsule once daily
Days 10 through 15: one 21-mg memantine HCl MR capsule once daily
Days 16 through 29: one 28-mg memantine HCl MR capsule once daily

Safety was assessed throughout the study by the monitoring of AEs, ECGs, vital sign assessments, physical examination, and laboratory evaluations.

Blood samples were obtained at the following times to determine memantine plasma concentrations:

Days 1, 27, and 28: 0.0 hour (predose)
Day 29: 0.0 hour (predose) and 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30, 48, 72, 96, 144, 192, and 240 hours postdose

ASSAY

Plasma samples were extracted, and quantification of memantine and its internal standard [redacted] was quantified following bioanalytical [redacted] using LC-MS/MS. The assay was linear in the concentration range of 0.5 to 100 ng/mL. Using 0.5 mL of plasma, the limits of quantification for memantine for this assay ranged from 0.5 ng/mL (lower limit of quantification) to 100 ng/mL.

During the study, the precision and accuracy of memantine standards were within 6.0% and ± 1.1%, respectively. The precision and accuracy of memantine quality control samples were within 6.7% and ± 1.3%, respectively. The performance of the method during the sample analysis is summarized in the Table below.

Table 2. Performance of the analytical [redacted] for plasma samples from study MEM-PK-18.

[redacted]	Accuracy & Precision	Quality Control Samples		
		1.50 ng/mL	20.00 ng/mL	80.00 ng/mL
Memantine	Accuracy (% Deviation)	0.0	0.1	-1.3
	Precision (% CV)	6.7	3.7	2.3

Memantine plasma samples (with EDTA present) were demonstrated to be stable for 319 days at -30°C and -70°C. Also it was demonstrated to be stable after 3 freeze/thaw cycles. For this particular study, the study period was from 06/15/2007-07/27/2007, and the plasma samples were analyzed from 10/01/2007 to 10/19/2007. From the time the first sample that was collected till the time the last sample was analyzed, the period lasted for about 4 months, shorter than the tested 319 days. Therefore, these stability data cover the period during which the study was conducted.

The total number of samples received for this study was 428, and all of them were analyzed. Two (2) out 428 samples were reanalyzed twice. The two reassayed values were consistent with each other, and neither of them agreed with the original values for both samples.

RESULTS:

Demographics

Table 3. Demographics of Healthy Subjects Enrolled in the Study (n=24)

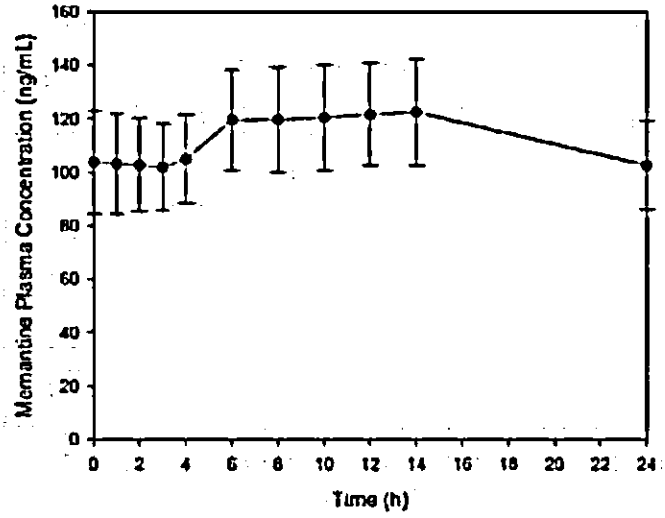
Age (Range)	Gender (n, %)	Weight (kg) (Range)	Race (n,%)	Ethnicity (n,%)
31.9±6.42 (18-45)	Male: 16 (66.7) Female: 8 (33.3)	69.96±8.95 (54.0-95.0)	Black: 1 (4.2) White: 23 (95.8)	Hispanic: 23 (95.) Non-Hispanic 1 (4.2)

A total of 24 subjects were enrolled and 20 subjects completed the study. PK parameters were only analyzed for 18 subjects because of vomiting in two subjects.

Pharmacokinetics

The principal PK parameters were derived from plasma concentrations using noncompartmental analysis in WinNonlin. The sponsor stated that concentrations below the limit of quantification were treated as zero for all PK calculations, and actual blood sampling times were used for PK analysis.

Figure 1. Mean (±SD) Memantine Plasma Concentrations vs Time Over the 24-hour Dosing Interval at Steady State Following Once-Daily Administration of a 28-mg Memantine HCl Modified-Release Capsule on Day 29



A summary of the PK parameters of memantine following a once-daily administration of 28 mg memantine HCl is presented in the table below. The rate of absorption of memantine from the MR capsule was slow with a median time of maximum plasma drug concentration (T_{max}) of 12 hours. The maximum plasma drug concentration (C_{max}) for memantine was only 24% higher than C_{min}.

Table 4. Steady-State Pharmacokinetic Parameters of Memantine Following a Once-Daily Oral Administration of a 28-mg Memantine HCl Modified-Release Capsule on Day 29

PK Parameter	Mean ± SD (N = 18)[a]
C_{max}, ng/mL	127.08 ± 21.09
T_{max}, h	11.1 ± 2.8 12.0 (6.0-14.0)[b]
$AUC_{0-\tau}$, ng•h/mL	2726 ± 430
C_{min}, ng/mL	102.52 ± 16.53
C_{av}, ng/mL	113.58 ± 17.92
$T_{\frac{1}{2}}$, h	55.7 ± 9.5
Swing	0.24 ± 0.07
Fluctuation	0.21 ± 0.05

[a] Subjects without vomiting. [b] Median (range).

Safety

There were no serious adverse events (SAEs) or deaths observed in the study. One subject discontinued from the study because of an AE (somnolence), one subject because of a protocol violation (subject not taking the study drug), and two subjects withdrew consent.

Overall, 49 treatment-emergent adverse events (TEAEs) were reported by 15 subjects during the course of the study. All AEs were mild in severity and most were possibly related to study drug. The most common TEAEs were headache, somnolence, and dizziness with incidence rates of 45.8%, 37.5%, and 16.7%, respectively.

CONCLUSIONS

Overall, once-daily administration of 28-mg memantine HCl MR capsule was safe and well tolerated. There were no deaths or SAEs in this study.

Memantine C_{max} was only 24% higher than C_{min}, indicating low variation in memantine plasma concentration levels over the steady-state dosing interval. The rate of absorption of memantine from the MR capsule was slow with a median T_{max} of 12 hours. Elimination half-life of memantine following administration of the MR capsule averaged 55.7 hours.

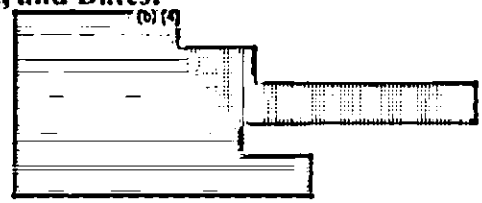
Reviewers' Comments

This study was a one-arm PK study, and it overlapped with study MEM-PK-23. Though from an NDA application point of view, this study was redundant and not needed, it was reviewed. OCP agrees that the pharmacokinetics of memantine XR at steady state were well characterized, and the targeted maintenance dose of 28 mg once daily was well tolerated in healthy volunteers.

3.1.5 Sprinkled vs Intact Bioequivalence Study

Open-label, Two-way Crossover, Single-Dose, Fasting Bioequivalence Study in Healthy Human Subjects Comparing Intact Administration of a Memantine HCl Extended-Release Capsule With Administration of Capsule Contents Sprinkled on Soft Food

Study Investigator, Site, and Dates:



Analytical Site and Dates:

Forest Research Institute
11/21/2008-12/17/2008

Study Number: MEM-PK-24

OBJECTIVE

To evaluate the bioequivalence of a memantine HCl extended-release (ER) capsule after oral administration as an intact capsule and after the capsule's contents were sprinkled on soft food (applesauce).

FORMULATIONS

Table 1. Products used in MEM-PK-18

	Manufacturer	Formulation	Lot #	Manufacture Date
Memantine HCl 28-mg trade ER capsule	Forest Laboratories, Inc.	28 mg Capsule	L0001965	10/2006

STUDY DESIGN

This was a single-center, randomized, open-label, 2-way crossover, single-dose study in a total of 30 healthy male and female subjects 18 to 45 years of age.

The strength of the ER capsule (28 mg) used in this study is the highest dosage strength of the ER capsule intended for the treatment of patients with moderate to severe Alzheimer's disease.

A total of 30 subjects were randomized to receive the following treatments separated by a 21-day washout period:

Treatment A: Single oral dose of one 28-mg memantine HCl ER capsule administered intact under fasted conditions

Treatment B: Single oral dose of one 28-mg memantine HCl ER capsule administered under fasted conditions after the capsule contents were sprinkled on 1 teaspoon of applesauce

Safety was assessed throughout the study by the monitoring of adverse events, electrocardiograms, vital sign assessments, physical examinations, and laboratory evaluations.

Blood was collected by a qualified phlebotomist via venipuncture of the antecubital vein from either arm using a pre-chilled 6-mL purple-topped Vacutainer tube (containing dipotassium ethylenediaminetetraacetic acid [K_2EDTA] as an anticoagulant) for determination of memantine concentrations in plasma. Blood samples were obtained at the following times to determine memantine plasma concentrations:

Days 1 and 22: 0.0 hour (predose) and 1, 2, 3, 4, 6, 8, 10, 14, 24, 30, 36, 48, 72, 96, 120, 144, 168, and 216 hours postdose

Blood samples were [redacted] and the plasma was harvested. After [redacted], the plasma samples were transferred into [redacted]

ASSAY

Plasma samples were extracted, and quantification of memantine and its internal standard $^2H_6$-memantine was quantified following bioanalytical [redacted] using LC-MS/MS. The assay was linear in the concentration range of 0.5 to 100 ng/mL. Using 0.5 mL of plasma, the limits of quantification for memantine for this assay ranged from 0.5 ng/mL (lower limit of quantification) to 100 ng/mL.

During the study, the precision and accuracy of memantine standards were within 8.1% and ± 2.1%, respectively. The precision and accuracy of memantine quality control samples were within 7.6% and ± 5.2%, respectively. The performance of the method during the sample analysis is summarized in the Table below.

Table 2. Performance of The Analytical [redacted] for Plasma Samples From Study MEM-PK-24.

Analyte	*Test*	*Plasma Quality Control Samples*		
		1.5 ng/mL	*20 ng/mL*	*80 ng/mL*
Memantine (including outliers)	Accuracy, % bias	-6.7	-5.6	-3.0
	Precision, % CV	11.4	5.2	4.8
Memantine (excluding outliers)	Accuracy, % bias	-4.1	-5.2	NA
	Precision, % CV	7.6	4.7	NA

Memantine plasma samples (with EDTA present) were found to be stable for 319 days at -30°C and -70°C. Also it was demonstrated to be stable after 3 freeze/thaw cycles. For this particular study, the study period was from 10/18/2008-11/17/2008, and the sample analysis date was from 11/21/2008 to 12/17/2008. From the time the first sample that was collected till the time the last sample was analyzed, the period lasted for about 2 months, shorter than the tested 319 days for stability. Therefore, these stability data cover the period during which the study was conducted.

The total number of samples received for this study was 1108, and all of them were analyzed. There were no PK reassays for memantine in this study.

RESULTS

Demographics

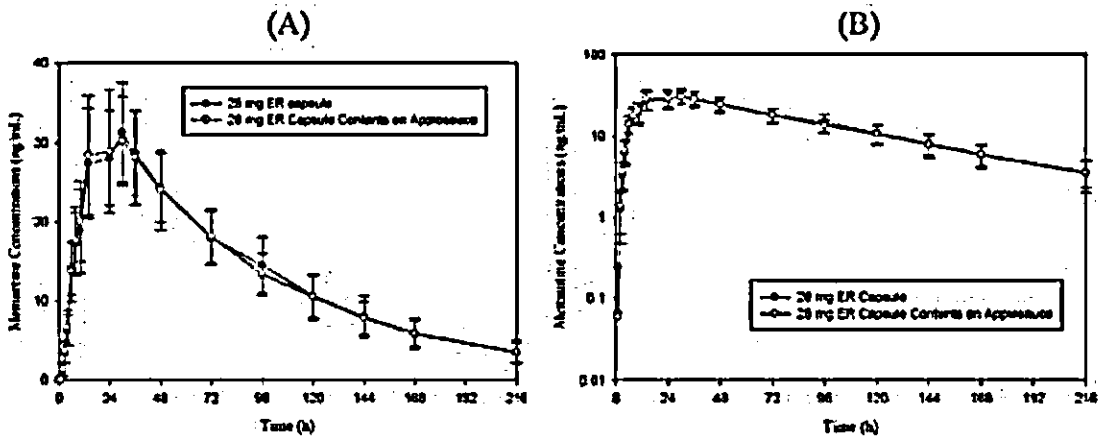
Table 3. Demographics of Healthy Subjects Enrolled in the Study (n=30)

Age (Range)	Gender (n, %)	Weight (kg) (Range)	Race (n,%)	Ethnicity (n,%)
29.1±7.8 (20-44)	Male: 6 (20) Female: 24 (80)	66.7±13.2 (49.0-99.3)	Black: 1 (4.2) White: 23 (95.8)	Hispanic: 10 (33.3) Non-Hispanic: 20 (66.7)

Pharmacokinetics

Following single-dose administration, the 90% CIs of the geometric mean ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (sprinkled/intact) were within the range of 80% to 125%, suggesting that the pharmacokinetics of memantine are not altered when the contents of a capsule are emptied onto soft food (applesauce) before administration. The rate of absorption of memantine from the ER capsule was slow, with a median T_{max} of about 30 hours for both treatments. No statistically significant differences in the T_{max} values were observed between the 2 treatments (p = 0.704).

Figure 1. Mean (± SD) Memantine Plasma Concentrations (ng/mL) Versus Time Following a Single Dose of a 28-mg Memantine ER Capsule Administered Intact (Treatment A) and Following a Single Dose of the Contents of an Identical Capsule Sprinkled on Applesauce (Treatment B) on a Linear (A) and Semilogarithmic (B) Scale



A summary of the single-dose PK parameters of memantine following the administration of a single 28-mg ER capsule intact (treatment A) or after the administration of a capsule's contents sprinkled on a teaspoon of applesauce (treatment B) is presented in the table below:

Table 4. Pharmacokinetic Parameters of Memantine After a Single Oral Administration of a 28-mg Memantine Extended-Release Capsule Taken Whole and of an Identical Capsule Taken With the Contents Sprinkled on a Teaspoon of Applesauce

PK parameters	Sprinkled on apple sauce (Mean ± SD) (n = 29)	Intact capsule (Mean ± SD) (n = 29)	Ratio of Geometric Means (%), Sprinkled/Intact	90% CI or p-Value
C_{max}, ng/mL	32.7± 7.2	31.9 ± 6.3	102.1	97.12-107.24
AUC_{0-t}, ng•h/mL	2930.8 ± 517.4	2949.1± 528.9	99.4	96.19-102.65
$AUC_{0-\infty}$, ng•h/mL	3264.2 ± 624.1	3267.2 ± 661.1	100	96.61-103.50
$T_{\frac{1}{2}}$, h	61.9 ± 11.8	58.7 ± 12.7	-	-
T_{max}, h	26.6 ± 7.7 30.0 (14.0-36.2)[a]	27.5 ± 8.0 30.0 (14.0-48.0)[a]	-	p = 0.704

[a]Median (range).

Safety

No serious adverse events (SAEs) or deaths were observed in the study. Overall, 31 treatment-emergent adverse events (TEAEs) were reported by 10 subjects during the course of the study. All but 2 of the TEAEs were mild in severity; the severity of the other 2 was moderate. About half of the incidents were possibly related to study drug.

The most common TEAEs were headache, insomnia, and abdominal cramping.

CONCLUSIONS

There were no deaths or SAEs in this study. The administrations of an intact 28-mg ER capsule of memantine and of the contents of an identical capsule sprinkled on applesauce were safe and well tolerated.

Following single-dose administration, the 90% CIs of the geometric mean ratios (sprinkled/intact) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were all within the range of 80% to 125%, suggesting that a memantine ER capsule may be administered either intact or with the contents of the capsule emptied onto soft food (applesauce) before administration. The rate of absorption of memantine from the ER capsule was slow, with a median T_{max} of about 30 hours for both treatments. No statistically significant differences in the T_{max} values were observed between the two treatments.

Reviewers' Comments

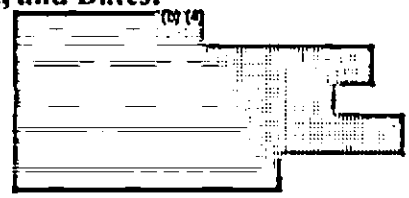
OCP agrees that memantine ER capsule emptied onto soft food (applesauce) before administration is bioequivalent to memantine ER capsule administered intact, when the highest strength of 28 mg was studied.

Thus, memantine ER capsule may be administered intact or sprinkled on applesauce.

3.1.6 Drug Interaction Study (memantine and bupropion)

A Single Centre, Randomized, Double-Blinded, Placebo-Controlled, Multiple Dose, Three-Period One-Sequence Cross-Over Study of the Pharmacokinetic Interaction of 30 mg Memantine on CYP2B6 with its Substrate Bupropion in Healthy Male Volunteers

Study Investigator, Site, and Dates:



Analytical Site and Dates:

Forest Research Institute
8/30/2006-9/15/2006

Study Number: MRZ 90001–0519/1

OBJECTIVE

1. To investigate the effect of memantine on CYP2B6 by the use of bupropion hydroxylation as a specific probe reaction for CYP2B6 activity.

2. To evaluate the pharmacokinetic interactions of bupropion and memantine.

FORMULATIONS

Table 1. Products used in MRZ 90001–0519/1

	Manufacturer	Formulation	Batch #	Manufacture Date
Placebo Tablet			6040203 (Bulk ware batch no: 2576203)	Not Available
Axura (Memantine HCl) 10-mg IR tablet 10mg, 20 mg, 30 mg per day	Forest Laboratories, Inc.	10 mg Tablet	6040203 (Bulk ware batch no: 50828)	Not Available
Wellbutrin (bupropion HCl) 100mg tablet			646678 (Batch no: Wellbutrin: A15662)	Not Available

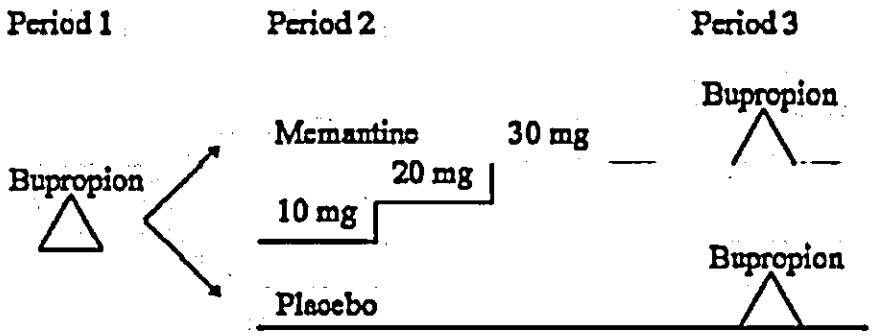
STUDY DESIGN

This was a single centre, randomized, double-blinded, placebo-controlled, multiple dose, three-period one-sequence cross-over study of the pharmacokinetic interaction of 30 mg memantine on CYP2B6 with its substrate bupropion in healthy male volunteers.

Memantine IR is given mostly in elderly patients at 20 mg memantine HCl daily (10 mg BID). After the same oral dose, healthy volunteers have a slightly lower systemic exposure to memantine as the target population of elderly volunteers in steady state. The dose of 30 mg is considered appropriate to reach the exposure in elderly treated with the recommended dose.

Randomized volunteers received a single dose of bupropion in Period 1 on Day 1. In Period 2, multiple doses of memantine (up-titration to 30 mg, steady state) or placebo were administered for 22 days and continued for further 4 days in Period 3. In Period 3 Day 1, another single dose of bupropion (100 mg) was administered concomitantly with multiple dose treatment of memantine or placebo.

Figure 1. Overall Study Design



Plasma concentrations of hydroxybupropion were determined after the single dose administration of bupropion alone and concomitantly with multiple dose treatment of memantine or placebo.

In steady state, plasma concentrations of memantine were determined when memantine was administered alone (Period 2, Day 22) and concomitantly with single dose treatment of bupropion (Period 3, Day1).

ASSAY

Plasma samples were extracted, and quantification of bupropion and 4-hydroxybupropion and its internal standard [redacted] was quantified following a validated LC-MS/MS.

The assay was linear in the concentration range of 0.25 to 200 ng/mL. The lower and higher limits of quantification for bupropion and 4-hydroxybupropion were 0.25 and 200 mg/mL, respectively.

A total of 720 human plasma samples were analyzed for bupropion and 4-hydroxybupropion content, and 31 samples were reanalyzed twice. For 2 (6.45%) of the samples, the reassayed values were not within 15% variation of the original value.

Table 2. Performance of The Analytical Method For Bupriopion And 4-Hydroxypropion For Plasma Samples From Study MRZ 90001–0519/1.

	Bupropion Quality Control Samples		
Concentration	0.75 ng/mL	7.5 ng/mL	150 ng/mL
Accuracy (% bias)	3.8	3.9	3.1
Precision (%CV)	4.8	4.2	4.2
	4-Hydroxybupropion Quality Control Samples		
Concentration	0.75 ng/mL	7.5 ng/mL	150 ng/mL
Accuracy (% bias)	4.8	1.8	3.4
Precision (%CV)	6.5	8.9	5.7

Memantine concentration was determined by a validated GC-MS method with a lower limit of quantification of 0.50 ng/mL. The assay was linear in the concentration range of 0.5 to 500 ng/mL. This method was also tested for selectivity, and no interference was observed in the presence of 500 ng/mL Bupropion and 1000 ng/mL 4-Hydroxybupropion.

Table 3. Performance of The Analytical Method For Memantine For Plasma Samples From Study MRZ 90001–0519/1.

	Quality Control Samples		
	1.5 ng/mL	25 ng/mL	400 ng/mL
Accuracy (% bias)	3.0	1.8	3.4
Precision (%CV)	9.0	10.2	9.5

A total of 416 plasma samples were analyzed for memantine, and 22 samples were reanalyzed. Based on the reassayed values, the variation for 54.6% (12/22) of the samples were more than 15%.

Genotyping was performed for the following genes: CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, and UGT1A1 using [redacted] gene sequencing.

RESULTS

Demographics:

Table 4. Demographics of Healthy Subjects Enrolled in the Study (n=24)

Age (Range)	Gender (n, %)	Weight (kg)	Race (n,%)
36.3±5.87 (27-44)	Male: 24 (100)	73.5±8.61	Caucasian: 24 (100)

Pharmacokinetics:

1. Hydroxybupropion

Figure 2. Geometric Mean of Hydroxybupropion Plasma Concentration-Time Profiles of the Memantine group of Period 1 (Bupropion) and Period 3 (Bupropion + Memantine)

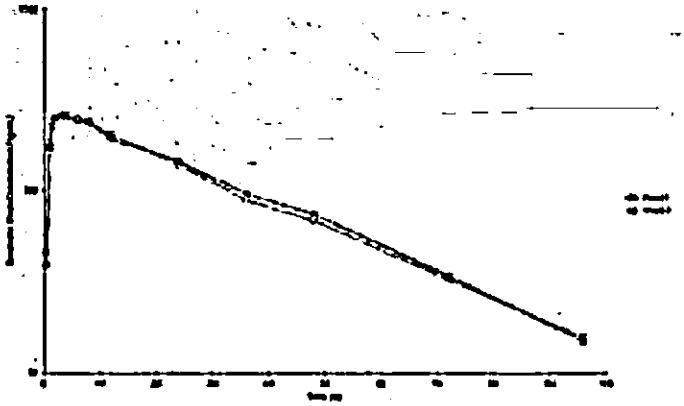


Table 5. Pharmacokinetic Parameters (Geometric Mean and CV (%)) of Hydroxybupropion in Period 1 (bupropion alone) vs Period 3 (Bup +Mem or Pla)

	Parameter	Period 1 (Bup alone)	Period 3 (Bup+Mem or Pla)
Memantine (n=16)	C_{max} (ng/mL)	265.08; 25.6%	272.98; 29.1%
	AUC_{0-t_z} (hr*ng/mL)	9071.1; 33%	9225.6; 31.9%
	$AUC_{0-\infty}$ (hr*ng/mL)	9713.7; 36.5%	9777.5; 33.3%
	T_{max} (hr)	3.0	4.0
	$T_{1/2}$ (hr)	23.7±6.01	23.1±3.97
Placebo (n=8)	C_{max} (ng/mL)	245.39; 32.5%	260.72; 23.6%
	AUC_{0-t_z} (hr*ng/mL)	8133.7; 35.5%	9194.2; 27.3%
	$AUC_{0-\infty}$ (hr*ng/mL)	8635.8; 37.2%	9800.6; 29.2%
	T_{max} (hr)	4.0	4.0
	$T_{1/2}$ (hr)	22.7±2.9	24.0±3.56

Median for T_{max}, mean ± SD for $T_{1/2}$. Bup: bupropion, Mem: memantine, Pla: placebo

Point estimates [90% CIs] of the ratios of $AUC_{0-\infty}$ and C_{max} of hydroxybupropion for the treatment contrast memantine+bupropion vs. bupropion were 100.7 [91.1; 111.2] and 103.0 [95.8; 110.6], respectively.

Table 6. Treatment Contrasts for Hydroxybupropion

Parameter	(Memantine + Bupropion) vs Bupropion	(Placebo + Bupropion) vs Bupropion
C_{max} [%]	103.0[95.8,110.6]	106.2[93.3,120.9]
$AUC_{0-\infty}$ [%]	100.7[91.1,111.2]	113.5[99.1,129.9]

2. Bupropion

Figure 3. Geometric Mean of Bupropion Plasma Concentration-Time Profiles of the Memantine group of Period 1 (Bupropion) and Period 3 (Bupropion + Memantine)

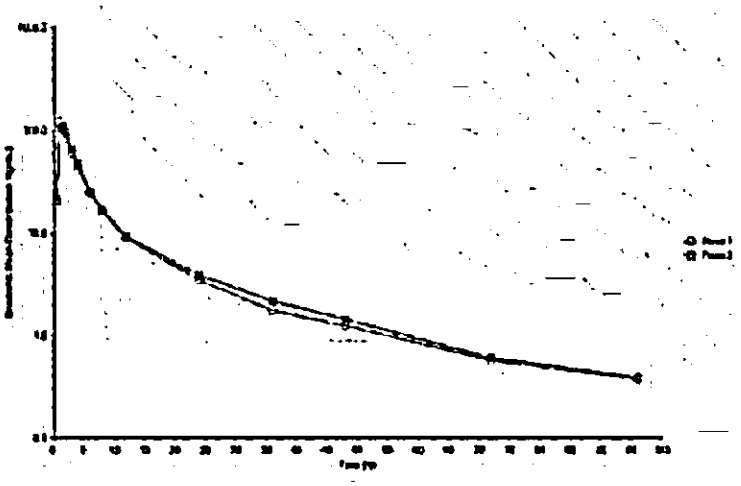


Table 7. Pharmacokinetic Parameters (geometric mean and CV (%)) of Bupropion in Period 1 (bupropion alone) vs Period 3 (Bup +Mem or Pla)

Treatment	Parameter	Period 1 (Bup alone)	Period 3 (Bup+Mem or Pla)
Memantine (n=16)	C_{max} (ng/mL)	122.9; 32.3%	127.16; 26.8%
	AUC_{0-tz} (hr*ng/mL)	599.3; 18.3%	646.7; 15.4%
	$AUC_{0-\infty}$ (hr*ng/mL)	612.0; 18%	658.4; 15.5%
	T_{max} (hr)	1.0	1.0
	CL_{tot}/f (mL/min)	2398±415.7	2221±334.7
Placebo (n=8)	C_{max} (ng/mL)	93.38; 49.5%	116.55; 40.9%
	AUC_{0-tz} (hr*ng/mL)	546.5; 38.5%	667.6; 36.1%
	$AUC_{0-\infty}$ (hr*ng/mL)	561.2; 37.3%	679.9; 35.6%
	T_{max} (hr)	1.0	1.25
	CL_{tot}/f (mL/min)	2724±940.8	2242±778.2

Median for T_{max}, mean ± SD for CL_{tot}/f; Bup: bupropion, Mem: memantine, Pla: placebo

Point estimates [90% CIs] of the ratios of $AUC_{0-\infty}$ and C_{max} of bupropion for the treatment contrast memantine+bupropion vs. bupropion were 107.6 [99.8; 116.0] and 104.0 [91.5; 118.2], respectively.

Table 8. Treatment Contrasts for Bupropion

Parameter	(Memantine + Bupropion) vs Bupropion	(Placebo + Bupropion) vs Bupropion
C_{max} [%]	104.0[91.5,118.2]	124.8[101.4,153.6]
$AUC_{0-\infty}$ [%]	107.6[99.8,116]	121.1[108,135.8]

3. Hydroxybupropion over bupropion

Table 9. Treatment Contrasts for the ratio of hydroxybupropion/bupropion

Parameters	(Memantine + Bupropion) vs Bupropion	(Placebo + Bupropion) vs Bupropion
Ratio of $AUC_{0-\infty}$ [%]	93.5[85.6,102.1]	93.7[85.4,102.9]
Ratio of C_{max} [%]	98.3[89.2,108.3]	84.6[69.5,103]

Point estimates [90% CIs] of the ratios of $AUC_{0-\infty}$ and Cmax of the individual ratios of hydroxybupropion over bupropion for the treatment contrast memantine+bupropion vs. bupropion were 93.5 [85.6; 102.1] and 98.3 [89.2; 108.3], respectively.

4. Memantine

Table 10. Pharmacokinetic parameters (geometric mean and CV (%)) of Memantine in Period 3 (bupropion+memantine) vs Period 2 (memantine alone)

Parameter	Period 3 (bupropion+memantine)	Period 2 (memantine)
$C_{max,ss}$ (ng/mL)	142.16; 17.9%	140.03; 18.7%
$C_{min,ss}$ (ng/mL))	90.84; 32.4%	88.42; 31.6%
$AUC_{0-\tau}$ (hr*ng/mL)	1474.5; 18.5%	1399.5; 20.6%
$T_{max,ss}$ (hr)	3.5	5.5
CL_{ss}/f (mL/min)	143.1±28.34	151.3±33.06
Median for T_{max}, and mean ± SD for CL_{tot}/f		

Point estimates [90% CIs] of the ratios of $AUC_{0-\tau}$ and $C_{max,ss}$ of memantine for the period contrast memantine+bupropion vs. memantine were 105.4 [100.9; 110.0] and 101.5 [95.2; 108.2], respectively.

Pharmacogenetics:

Rapid metabolizers (as predicted from genotyping) were clearly distinguishable regarding their ratio of $AUC_{0-\infty}$ of hydroxybupropion over bupropion compared to predicted normal, normal/slow and slow metabolizers which – phenotypically – could not be clearly distinguished from each other.

The proportion of rapid metabolizers was similar in both groups, i.e. 2 of 16 (12.5%) in the memantine group and 1 of 8 (12.5%) in the placebo group.

Table 11. Individual CYP2B6 Phenotype and AUC0-∞ of Hydroxybupropion and Bupropion in Period 1

Volunteer No.	CYP2B6 Phenotype	Treatment Group	$AUC_{0-\infty}$ (hr*ng/ml)		Ratio of $AUC_{0-\infty}$
			Hydroxybupropion	Bupropion	Hydroxybupropion over bupropion
510	SM	Memantine	14542	854	17.0
516	SM	Memantine	8649	655	13.2
517	SM	Memantine	11042	650	17.0
519	SM	Placebo	11628	898	12.9
501	SM/NM	Memantine	8684	825	10.8
502	SM/NM	Memantine	5323	486	11.0
503	SM/NM	Memantine	6157	694	8.9
511	SM/NM	Placebo	4515	488	9.3
512	SM/NM	Memantine	7804	620	12.6
513	SM/NM	Memantine	10234	732	14.0
520	SM/NM	Memantine	6764	602	11.2
504	NM	Placebo	8157	477	17.1
505	NM	Placebo	9291	761	12.2
507	NM	Memantine	13581	654	20.8
508	NM	Memantine	7978	536	14.9
509	NM	Placebo	14107	877	16.1
514	NM	Placebo	8611	425	20.3
515	NM	Placebo	6159	493	12.5
518	NM	Memantine	12213	591	20.7
522	NM	Memantine	9917	512	19.4
524	NM	Memantine	8406	522	16.1
506	RM	Memantine	11935	470	25.4
521	RM	Memantine	21845	539	40.5
523	RM	Placebo	10390	337	30.8

SM: slow metabolizer; NM: normal metabolizer; RM: rapid metabolizer

Safety

A total of 17 volunteers experienced 83 treatment emergent adverse events (treatment duration): 7 events in 5 volunteers when bupropion was administered alone (4 or 5 days), 56 events in 11 volunteers when memantine was administered alone (22 days), 7 events in 5 volunteers when memantine was administered concomitantly with bupropion (5 days), and 13 events in 4 volunteers when placebo was administered alone (22 days).

All treatment emergent adverse events were of mild (68 events in 16 volunteers) or moderate (14 events in 5 volunteers) intensity, except one of which was of severe (dizziness in 1 volunteer) intensity. The latter was most probably related to the procedure of blood sampling.

Adverse drug reactions with an incidence or frequency ≥2:

When memantine was administered alone: asthenia (4 events in 1 volunteer), fatigue (2 events in 2 volunteers), muscular weakness (2 events in 1 volunteer), disturbance in attention (4 events in 1 volunteer), headache (7 events in 5 volunteers), dizziness (9 events in 4 volunteers). When placebo was administered alone: chest discomfort (2 events in 1 volunteer), headache (3 events in 2 volunteers), aggression (2 events in 1 volunteer).

CONCLUSIONS

No influence of memantine on CYP2B6 activity (hydroxylation of bupropion) was found, and no interaction of bupropion on the pharmacokinetics of memantine was observed either.

The safety data analyzed in this study did not reveal new safety concern regarding memantine alone or the combination with bupropion.

Reviewers' Comments

OCP agrees with the sponsor's conclusions that memantine did not affect the activity of CYP2B6, and bupropion did not affect the pharmacokinetics of memantine in vivo. Memantine and bupropion can be taken concomitantly.

3.1.7 In Vitro Alcohol Dose-Dumping Study

In Vitro Evaluation of Alcohol Induced Dose-Dumping in Memantine ER (Extended-Release) Capsules 7mg, 14mg, 21mg and 28mg

Study Number: PRD-RPT-ANL-00209

OBJECTIVE

To evaluate the effect of various concentrations of alcohol on the dose dumping potential of memantine HCl ER capsules: 7 mg, 14 mg, 21 mg, 28 mg strengths.

FORMULATIONS

Table 1. Products used in PRD-RPT-ANL-00209

	Manufacturer	Formulation	Batch #	Expiration Date
Memantine ER 7 mg capsule	Forest Laboratories, Inc.	7-mg Capsule	BN0014793	Not Available
Memantine ER 14 mg capsule	Forest Laboratories, Inc.	14-mg Capsule	BN0014795	Not Available
Memantine ER 21 mg capsule	Forest Laboratories, Inc.	21-mg Capsule	BN0014564	Not Available
Memantine ER 28 mg capsule	Forest Laboratories, Inc.	28-mg Capsule	BN0001692	Not Available

STUDY DESIGN

The dissolution procedure used in this dose-dumping study was done in pH1.2NaCl/HCl medium (simulated gastric TS without pepsin). The dissolution testing parameters are summarized in the table below.

Table 2. In Vitro Dissolution Testing Parameters

Number of Units	n=12 capsules used for each test
Apparatus	USP 1 (baskets)
Rotation Speed	100 RPM
Total Volume	900 mL
Sample Intervals	15,30,45,60,75,90,105,120 and 150 min without replacement of media
Medium	pH1.2 NaCl/HCl
Test1- Test2- Test3- Test4	Medium (control) Medium with 5% v/v Alcohol, USP Medium with 20% v/v Alcohol, USP Medium with 40% v/v Alcohol, USP

The same dissolution procedure was used by the sponsor for regular dissolution testing.

ASSAY

Memantine HCl in the dissolution samples was quantitated through a reverse-phase HPLC method. The amount is determined through the use of an external memantine HCl standard.

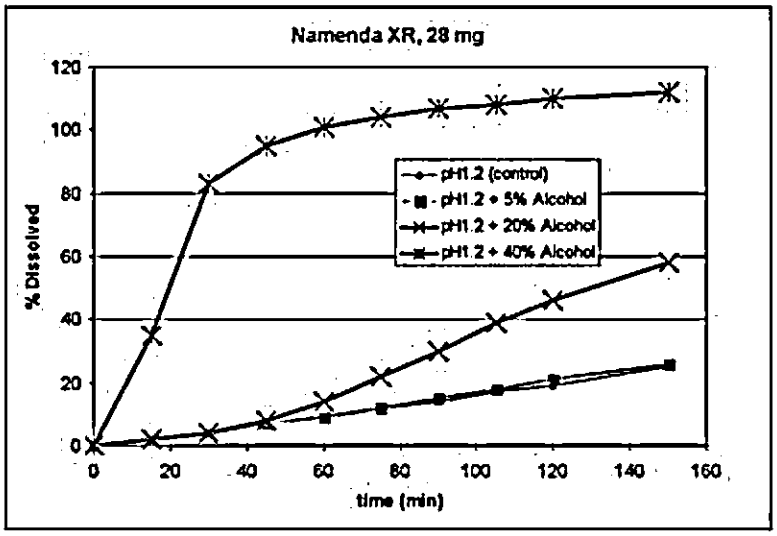
RESULTS

For the 28-mg strength, no dose dumping was observed with 5% alcohol relative to the control. Minimal dose dumping occurred with 20 % alcohol, with a mean of 14% of the capsule dissolved at one hour (the control was 9%), but dose dumping has occurred at 2 hrs, with a mean of 46% of the capsule dissolved (the control was 19%). In tests using 40% alcohol, dose dumping was more pronounced, with a mean of 95% of the capsule dissolved at 45 minutes (the control was 7%). These results indicate that nearly the entire capsule dose of 28 mg would be released in 30-45 minutes in a 40% alcohol environment.

Table 3. Dissolution Results of Memantine HCl (28-mg Strength) in pH1.2 Medium With Different Percentage of Alcohol (%)

Time (min)	0%	5%	20%	40%
0	0	0	0	0
15	2	2	2	35
30	4	4	4	83
45	7	7	8	95
60	9	9	14	101
75	12	12	22	104
90	14	15	30	107
105	17	18	39	108
120	19	21	46	110
150	25	26	58	112

Figure 1. Dissolution of 28-mg Memantine ER (Namenda XR) in pH1.2 medium in the presence of various concentrations of alcohol



For the lower strengths of memantine ER capsules (21-mg, 14-mg, 7-mg), they showed similar dissolution profiles to the 28-mg strength.

Table 3. Dissolution Results of Memantine HCl in pH1.2 Medium With Different Percentage of Alcolhol (%)

	21 mg				14 mg				7 mg			
Time (min)	0%	5%	20%	40%	0%	5%	20%	40%	0%	5%	20%	40%
0	0	0	0	0	0	0	0	0	0	0	0	0
15	2	2	1	31	1	1	2	40	1	2	2	34
30	4	4	3	76	3	3	4	78	3	4	4	77
45	6	7	7	87	5	5	7	88	5	6	7	91
60	8	9	12	93	8	7	13	92	7	9	13	98
75	10	12	19	96	10	10	21	95	9	11	21	101
90	13	15	28	98	13	13	29	97	11	14	29	103
105	15	18	36	100	15	15	37	99	14	17	37	105
120	18	21	43	100	18	18	44	100	17	19	45	106
150	21	26	55	102	23	24	55	101	19	25	56	107

Reviewers' Comments

Moderate dose-dumping effect of ethanol on memantine ER capsule was observed in 20% v/v alcohol, and pronounced effect was observed in 40% v/v ethanol, for all dose strengths.

The extreme situation of dose dumping with 40% alcohol means that the entire capsule dose of 28 mg would be released in 30-45 minutes, i.e., ER is behaving as an IR. Based on simulation, 28 mg XR QD and 28 mg IR QD have comparable concentration at steady state. Single 40 mg doses of memantine were safe and well tolerated. In order to understand the impact of a patient receiving a bolus of memantine 28 mg, the sponsor has looked at the adverse events for memantine in worldwide post marketing and clinical trials experience for doses up to 100 mg. The majority of the events included dizziness, somnolence, confusion, vertigo, weakness and vomiting. There were no deaths in overdoses up to 100 mg. Further, data from clinical trials for other indications where the daily dose was over 20 mg, reaching up to 100 mg, revealed the same events as mentioned above, and were mild in intensity and reversible. Overall, the events were mild and reversible. Efficacy will not be decreased with one incidence or infrequent consumption of alcohol. Thus, there is no concern about alcohol consumption from a clinical pharmacology standpoint.

3.2 Pharmacometric Review

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1. Is the sponsor proposed switching dosing regimen justified?

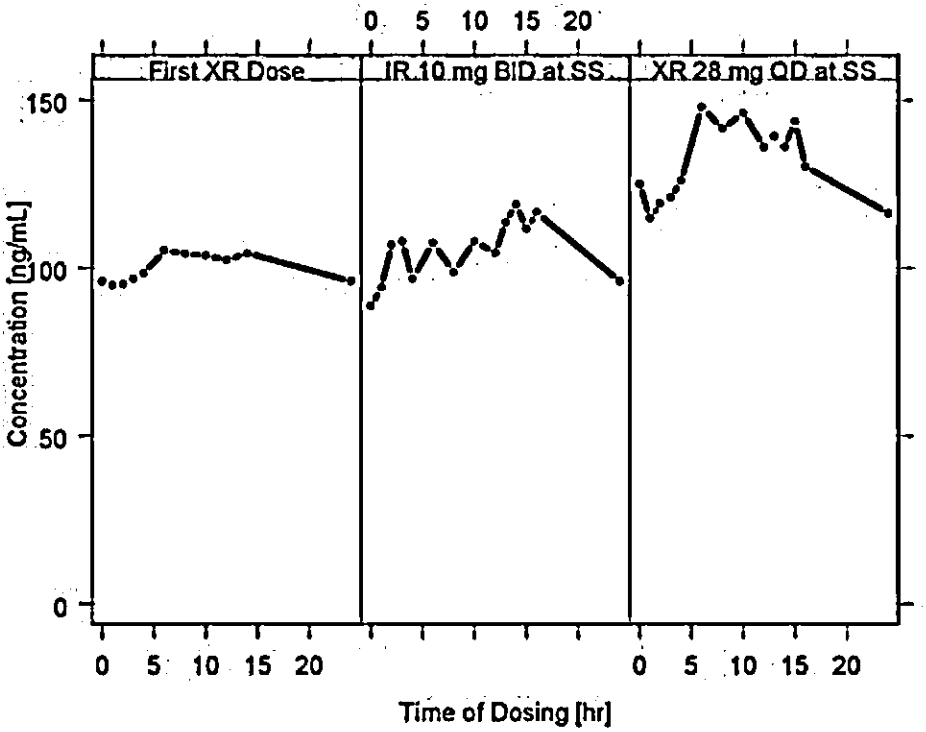
Yes. The sponsor proposed switching dosing regimen is justified from clinical pharmacology's perspective. Following the sponsor's proposal, a patient who is stabilized with NAMENDA ® IR formulation 10 mg twice daily may directly switch to XR formulation at a dose of 28 mg once daily with no additional titration or lag time.

Similar memantine exposure can be achieved immediately after the formulation change. A comparison between the steady state memantine PK profiles using 10 mg BID dosing of IR formulation and the memantine PK profile following the first switched dose (28 mg QD) of XR formulation was made. As shown in Figure 1, the mean steady state concentration within 24 hours following10 mg BID dosing of IR formulation was in a range between 88.7 and 118.8 ng/mL. Our simulation indicated that memantine concentration was in a range of 94.9-105.3 ng/mL on Day 1 after the formulation switching. It is clear that similar memantine exposure can be achieved on Day 1 following the formulation switching. Therefore, the efficacy, tolerability and safety profiles were expected to be similar prior to and immediately after the formulation switching.

Following long-term treatment of 28 mg QD XR formulation, the mean memantine exposure gradually increased to the range of 114.9 – 147.8 ng/mL (shown in Figure 4 based on Day 29 data). With higher exposure than that achieved using 10 mg BID dosing of IR formulation, efficacy was expected to be achieved / maintained. The results from the pivotal trial (Study MEM-MD-50) further confirm that treatment benefit can be achieved using 28 mg QD dosing of XR formulation in patients with moderate to severe dementia of Alzheimer's type.

Short-term and long-term safety profile following the treatment of 28 mg QD formulation was further evaluated in a dedicated phase III clinical trial (Study MEM-MD-51). In Study MEM-MD-51, a total of 36 patients who were receiving memantine IR 10 mg twice daily for at least 30 days before screening were switched to memantine ER 28 mg daily. Among them, 19.4% discontinued the trial. The incidence of therapeutic emerging adverse events (TEAE) for this group of patient was 91.7% with the incidence of severe adverse events (SAE) of 27.8%. The incidences were similar between the patients who switched formulations and patients who initialed with XR formulation.

Figure 1 Mean Memantine PK Profiles Following IR and XR Formulations



Note:

IR 10 mg BID at SS = Steady state memantine concentration following 10 mg BID dosing of IR formulation

First XR Dose = Memantine concentration following the first dose of 28 mg XR formulation in patients who were stabilized using 10 mg BID IR formulation

XR 28 mg QD at SS = Steady state memantine concentration following 28 mg QD dosing of XR formulation

1.2 Recommendations

None.

2 PERTINENT REGULATORY BACKGROUND

The submission dated on 20 August 2009 is an original submission for Namenda ® (Memantine Hydrochloride) XR capsule (once daily) 7 mg, 14 mg, 21 mg and 28 mg for the treatment of moderate to severe dementia of the Alzheimer's type. The immediate release (IR) formulation that was approved by the agency on Oct 16, 2003 under NDA

21487 requires twice daily dosing (10 mg BID). The new formulation utilizes an extended release technology to achieve a target dose of 28 mg once daily.

The safety and efficacy of Namenda ® XR was demonstrated from one pivotal phase III placebo-controlled study (Study MEM-MD-50) and three open-label safety studies (MEM-MD-51, MEM-MD-54, and MEM-MD-82). Efficacy was demonstrated in Study MEM-MD-50 based on the results of the coprimary efficacy assessments, the Severe Impairment Battery (SIB), and the Clinician Interview-Based Impression of Change With Caregiver Input (CIBIC-plus). Patients who completed Study MEM-MD-50 could be enrolled in Study MEM-MD-54. MEM-MD-51 was an open-label 1-year safety study that included both treatment-naïve patients (Group 1) and patients who were receiving memantine IR 10 mg BID (Group 2). The Group 2 results suggest patients who receive memantine IR 10 mg BID can safely switch to memantine ER 28 mg/d with good tolerability. Patients who completed Study MEM-MD-51 or Study MEM-MD-54 could be enrolled in Study MEM-MD-82, which is ongoing. Results from seven completed studies using memantine immediate-release (IR) provide additional exposure data. Further PK and safety information can be obtained from four completed clinical pharmacology studies using both memntine XR and memantine IR formulations.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Study MEM-PK-23:

Study MEM-PK-23 is a cross-over Phase I study designed to evaluate the memantine pharmacokinetics following single and multiple dose of IR and XR formulations in healthy subjects. A total of 26 subjects were enrolled in the study to receive IR and XR formulations with a 21-day washout period (Figure 2). Blood samples were collected at various time points following the treatment (Figure 3). A summary of the single-dose PK parameters of memantine following administration of a single 10-mg IR tablet or a single 28-mg ER capsule is presented in Table 1. Following a single dose administration, the dose-normalized maximum plasma drug concentration (C_{max}/D) value for the ER formulation was reduced by 34% compared with that of the IR treatment. The T_{max} was significantly longer following administration of the ER (26.11 ± 9.39 hours) than with the IR formulation (5.90 ± 2.45 hours). In addition, a summary of the steady-state PK parameters of memantine following a once-daily administration of 28 mg memantine HCl ER capsule and IR tablet is presented in Table 2. The rate of memantine absorption at steady state following once-daily administration of memantine HCl ER capsule was slower (T_{max} of 9.5 hours) compared with that following twice-daily administration of memantine IR tablet (T_{max} of 6.6 hours). Mean $C_{max,SS}$, AUC_{0-24}, and $C_{min,ss}$ of memantine at steady state following administration of memantine HCl ER capsule were 163 ng/mL, 3058 ng•h/mL, and 114 ng/mL, respectively, and were 48%, 33% and 16% greater than the corresponding values following administration of the memantine IR tablet (based on ratio of geometric means from ANOVA). Fluctuation in the plasma levels of memantine over the steady-state dosing interval was slightly greater for the ER (37%) compared with the IR (15%) dosing regimen. Elimination half-life averaged 58.5 hours (range, 43-83 hours) and 56.7 hours (range, 47-75 hours) for the IR tablet and ER

capsule, respectively, and were both similar to historical data for the IR tablet (Namenda, 2007).

Figure 2 A Summary of Treatment Arm

Treatment A		
	Day 1:	Single 10-mg IR tablet under fasted conditions
	Days 4-9:	5-mg IR tablet BID
	Days 10-15:	10-mg IR tablet in the morning and 5 mg IR tablet in the evening
	Days 16-28:	10-mg IR tablet BID
	Day 29:	10-mg IR tablet BID (morning dose under fasted conditions)
Treatment B		
	Day 1:	Single 28-mg ER capsule under fasted conditions
	Days 4-9:	14-mg ER capsule once daily
	Days 10-15:	21-mg ER capsule once daily
	Days 16-28:	28-mg ER capsule once daily
	Day 29:	28-mg ER capsule under fasted conditions

Figure 3 Sampling Schedule

Days 1 and 51:	0.0 hour (predose) and 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, and 72 hours (postdose)
Days 27, 28, 77, and 78:	0.0 hour (predose)
Days 29 and 79:	0.0 hour (predose) and 1, 2, 3, 4, 6, 8, 10, 12, 13, 14, 15, 16, 24, 48, 72, 96, 144, and 192 hours (postdose)

Table 1 Pharmacokinetic Parameters of Memantine After Single Oral Administration of either 10-mg Immediate-Release (Treatment A) Memantine HCl Tablet or 28-mg Extended-Release (Treatment B) Memantine HCl Capsule

PK Parameter	*10-mg IR Tablet, Mean ± SD (N = 20)*	*28-mg ER Capsule, Mean ± SD (N = 20)*	*Ratio of Geometric Means, %*	*90% CI or p-Value*
C_{max}, ng/mL	16.04 ± 3.89	29.66 ± 7.56	—	—
C_{max}/D, ng/mL/mg	1.60 ± 0.39	1.06 ± 0.27	64.9	59.53-70.84
AUC_{0-72}, ng•h/mL	695.64 ± 149.58	1515.86 ± 431.29	—	—
AUC_{0-72}/D, ng•h/mL/mg	69.56 ± 14.96	54.14 ± 15.40	75.4	68.66-82.89
T_{max}, h	5.90 ± 2.45 6.0 (2.0-10.0)[a]	26.11 ± 9.39 30.0 (8.0-36.0)[a]	—	p < .0001

a Median (range).

AUC_{0-72} = area under the plasma concentration versus time curve from time zero to 72 hours at steady state; AUC_{0-72}/D = dose-normalized AUC_{0-72}; C_{max} = maximum plasma drug concentration; C_{max}/D = dose-normalized C_{max}; ER = extended release; IR = immediate release; T_{max} = time of maximum plasma drug concentration.

Table 2 Mean Steady-State Pharmacokinetic Paramcters of Memantine on Day 29 Following Administration of either 10-mg IR (Treatment A) Memantine HCl Tablet or 28-mg ER (Treatment B) Memantine HCl Capsule

PK Parameter	*10-mg IR Tablet, Mean ± SD (N = 20)*	*28-mg ER Capsule, Mean ± SD (N = 20)*	*Ratio of Geometric Means, %*	*90% CI or p-Value*
$C_{max,ss}$, ng/mL	109.19 ± 36.62	163.06 ± 68.17	147.9	134.51-162.66
$C_{min,ss}$, ng/mL	95.90 ± 27.19	113.54 ± 35.19	116.4	104.23-130.01
C_{av}, ng/mL	93.46 ± 25.50	127.41 ± 34.73	—	—
AUC_{0-t}, ng·h/mL	1121.47 ± 306.06	3057.87 ± 833.39	—	—
AUC_{0-24}, ng·h/mL	2324.62 ± 652.68	3057.87 ± 833.39	132.7	123.08-143.13
$T_{½}$, h	58.47 ± 10.88	56.69 ± 8.44	—	—
$T_{max,ss}$, h	6.59 ± 3.71 7.0 (2.0-11.95)[a]	9.45 ± 3.79 9.0 (6.0-16.0)[a]	—	p = 0.100
Swing	0.15 ± 0.12[b]	0.48 ± 0.50	—	—
Fluctuation	0.15 ± 0.11[b]	0.37 ± 0.29	—	—
AI	7.27 ± 1.42	4.62 ± 1.34	—	—
CL/F, L/h	7.87 ± 1.83	8.20 ± 2.38	—	—

a Median (range).
b N = 17.
AI = accumulation index; $AUC_{0-t,ss}$ = area under the plasma concentration versus time during the dosing interval t at steady state; C_{av} = average steady-state plasma drug concentration; CL/F = oral plasma clearance; $C_{max,ss}$ = maximum plasma drug concentration at steady state; $C_{min,ss}$ = minimum plasma drug concentration at steady state; PK = pharmacokinetic; $T_{½}$ = terminal elimination half-life; $T_{max,ss}$ = time of maximum plasma drug concentration following administration at steady state.

4 REVIEWER'S ANALYSIS

4.1 Introduction

Following the sponsor's proposal, a patient who is stabilized with NAMENDA ® IR formulation 10 mg twice daily may directly switch to XR formulation at a dose of 28 mg once daily. The reviewer's analyses were conducted to understand whether the proposed switching dosing regimen can be justified.

4.2 Objectives

The objective for the reviewer's analyses was:

1. To understand whether the proposed switching dosing regimen can be justified based on the clinical trial results.

4.3 Analyses Methods and Results

4.3.1 Data Sets

Data sets used were summarized in Table 3.

Table 3. Analysis Data Sets

Study Number	Name	Link to EDR
Study MEM-PK-23	Plconc.xpt	\\Cdsesub1\evsprod\NDA022525\0000\m5\datasets\mem-pk-23\analysis

4.3.2 Software

Analyses were performed by using S_Plus (Version 7.0 for Windows, Insightful)

4.3.3 Models and Results

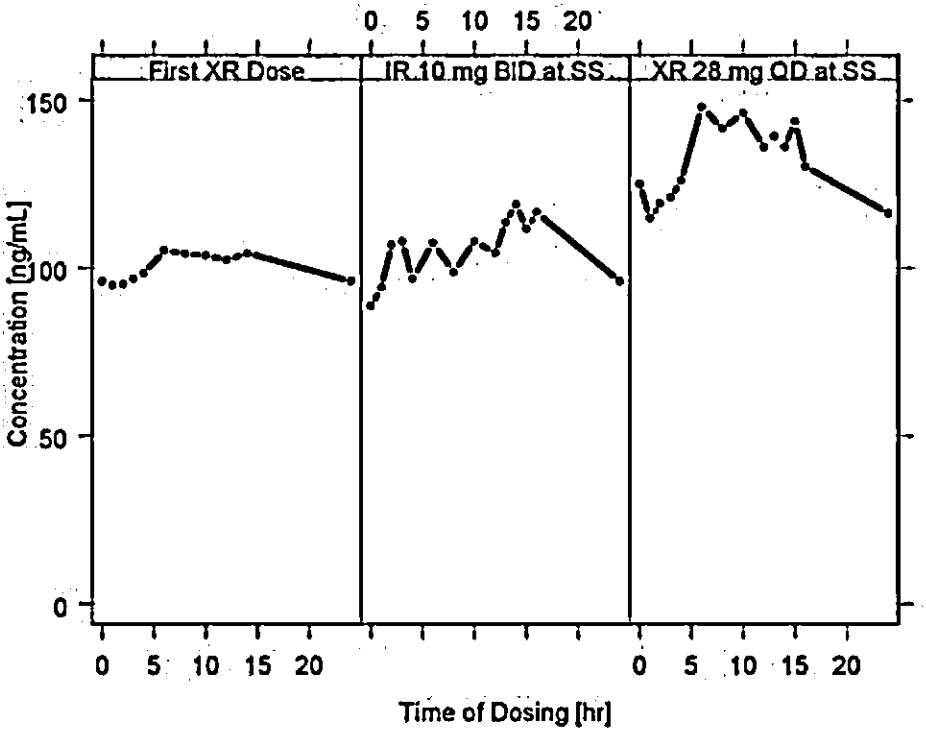
The reviewer's analyses were performed to understand whether the sponsor proposed switching dosing regimen can be justified based on clinical trial results.

Firstly, we compared the steady state memantine PK profiles using 10 mg BID dosing of IR formulation with the memantine PK profile following the first switched dose (28 mg QD) of XR formulation. The data from Study MEM-PK-23 was applied for comparison. The mean steady state PK profile collected on Day 29 following10 mg BID dosing of IR formulation was shown in Figure 4. The concentration was in a range between 88.7 and 118.8 ng/mL. The memantine PK profile following the first dose of 28 mg XR formulation was simulated by superimposing the residual concentration from the IR formulation with the concentration of the first dose of 28 mg XR formulation. The simulation indicated that memantine concentration was in a range of 94.9-105.3 ng/mL on Day 1 after the formulation switching. It is clear that similar memantine exposure can be achieved on Day 1 following the formulation switching. Therefore, the efficacy, tolerability and safety profiles were expected to be similar prior to and immediately after the formulation switching.

Secondly, following long-term treatment of 28 mg QD XR formulation, the mean memantine exposure gradually increased to the range of 114.9 – 147.8 ng/mL (shown in Figure 4 based on Day 29 data). With higher exposure than that achieved using 10 mg BID dosing of IR formulation, efficacy was expected to be achieved / maintained. The results from the pivotal trial (Study MEM-MD-50) further confirm that treatment benefit can be achieved using 28 mg QD dosing of XR formulation in patients with moderate to severe dementia of Alzheimer's type.

Thirdly, the short-term and long-term safety profile following the treatment of 28 mg QD formulation was further evaluated in a dedicated phase III clinical trial (Study MEM-MD-51). In Study MEM-MD-51, a total of 36 patients who were receiving memantine IR 10 mg twice daily for at least 30 days before screening were switched to memantine ER 28 mg daily. Among them, 19.4% discontinued the trial. The incidence of therapeutic emerging adverse events (TEAE) for this group of patient was 91.7% with the incidence of severe adverse events (SAE) of 27.8%. The incidences were similar between the patients who switched formulations and patients who initialed with XR formulation.

Figure 4 Mean Memantine PK Profiles Following IR and XR Formulations



Note:

IR 10 mg BID at SS = Steady state memantine concentration following 10 mg BID dosing of IR formulation

First XR Dose = Memantine concentration following the first dose of 28 mg XR formulation in patients who were stabilized using 10 mg BID IR formulation

XR 28 mg QD at SS = Steady state memantine concentration following 28 mg QD dosing of XR formulation

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\

6 APPENDIX

None

3.3 DSI Inspection Report

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 26, 2010

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products

FROM: Xikui Chen, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 3/26/10
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-525, Namenda XR (Memantine HCl) Extended Release Capsules, 28 mg, Sponsored by Forest Laboratories, Inc.

At the request of the Division of Neurology Products, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study MEM-PK-17: "A Randomized, Open-Label, Three-Way Crossover, Single-Dose Bioequivalence and Food-Effect Study of the Clinical Formulation and the to-Be-Marketed Modified-Release Formulation of Memantine HCl in Healthy Human Subjects"

The clinical portion of this study was conducted at [redacted] Following the inspection of [redacted] (3/15-19/10), no Form FDA 483 was issued. The analytical portion was conducted at Forest Research Institute, Farmingdale, NY. Following the inspection of Forest Research Institute (3/8-12/10), Form FDA-483 was issued (Attachment 1). Our evaluation of the inspectional findings and the firm's response dated March 23, 2010 (Attachment 2) follows:

1. The firm failed to document the preparations of the memantine calibration standards in analytical runs 7 to 30, and 32.

Page 2 of 3 - NDA 22-525, Namenda XR (Memantine HCl) Extended Release Capsules, 28 mg
During the inspection, DSI scientist noted that spiking solutions used to prepare calibration standards were referenced in a 'Sample Analysis' Form in Lab Notebooks 2590 and 2598. However, Forest Research Institute did not maintain any source records related to the preparation of calibration standards used in all analytical runs for the determination of memantine concentrations in subject plasma samples (i.e., runs 7-30, and run 32). For example, there were no records concerning date and time the calibration standards were prepared, no records on volume of spiking solution used, and no records of any dilution step or intermediate steps involved in the preparation process. Due to this observation, DSI could not verify the actual preparation of the calibration standards. Thus, the integrity and validity of all standard curves generated in analytical runs of study plasma samples can not be confirmed.

In their response, Forest Research Institute acknowledged the observation but explained that Study MEM-PK-17 was an old study conducted in 2007. Since the last FDA inspection in 2009, Forest Research Institute improved the documentation for fresh preparation of calibration standards for stability evaluations, effective June 16,2009. This response, however, does not resolve the DSI concern cited above.

OCP Comments:

There were (b) (4) *steps identified in the preparation of the plasma standard curve for memantine* (b) (4) *All these above steps were recorded in the Sponsor's notebook. However, the last step where* (b) (4) *was found by DSI as not having been documented in the notebook. They do have chromatograms for these standard curves.*

In an email between DSI and the Sponsor, the latter clearly stated that they did not make an explicit notebook entry for the last step, but that they intended to follow the standard operating procedure for making fresh daily preparations of the plasma standard curve solutions. Further, the sponsor has acknowledged that since June 2009 their documentation practice regarding the bioanalytical analysis has been improved.

OCP accepts the Sponsor's response.

2. The firm failed to follow [redacted] SOP-00039 (version 5.0) for a pharmacokinetic (PK) re-assay of subject 0001 in treatment C at 2 hour.

The re-assay of the plasma sample from subject 0001 in treatment C at 2 hour was a deviation from [redacted] SOP-00039 entitled "Re-assay of Biological Samples" (version 5.0). However, the re-assay value confirmed the original assay value, and thus there is no significant impact on the study outcome.

In their response, Forest Research Institute acknowledged that this re-assay request was an error.

OCP Comments:

Sponsor's response is acceptable to OCP.

3. There is a discrepancy in the study report MEM-PK-17 concerning the total number of samples received and analyzed. Section 9.5.2.3 lists 1328 samples however, section 9.5.2.4 lists 1348 samples.

Based on the sample receiving source records (456 samples, 455 samples and 437 samples were received by the firm), the correct total number of samples received by the firm should be 1348 samples. Forest Research Institute states that all the received samples were analyzed.

In their written response, Forest Research Institute said the total receipt of 1328 samples reported in Section 9.5.2.3. of the study report was an typographical error.

OCP Comments:

Sponsor's response is acceptable to OCP.

Conclusion:

The integrity and validity of all standard curves used in the analysis of study subject plasma samples in Study MEM-PK-17 car not be confirmed as the source records related to the preparation of calibration standards were not maintained at Forest Research Institute and were not available for FDA audit (see discussion in 483 Item 1).

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Xikui Chen, Ph.D.

Final Classification:

NAI - [redacted]
VAI - Forest Research Institute, Farmingdale, NY

cc: DARRTS
DSI/Salewski/Yau/Chen/Rivera-Lopez/CF
HFD-120/Teresa Wheelous/Russell Katz/Ranjit Mani
HFD-860/Raman Baweja
HFR-SE250/Brunilda Torres (BIMO)
HFR-NE1500/Thomas Hansen (BIMO)
HFR-SE2560/Dianiris Ayala
HFR-NE1500/ Robert Steyert

cc: email
CDER DSI PM TRACK
Draft: XC 3/24/10
Edit: MKY 3/25/10;
DSI 6012_O:\BE\EIRCover\22525.for.mem.doc
FACTS [redacted]

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.4 OCP's Labeling for Namenda XR

3.5 Filing report

6.1.1 Office of Clinical Pharmacology and Biopharmaceutics

7 *NEW DRUG APPLICATION FILING AND REVIEW FORM*

7.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	22-525	Brand Name	Namenda (b)(4)
OCPB Division (I, II, III)	OCP1	Generic Name	Memantine HCL
Medical Division	Neurology	Drug Class	NMDA receptor antagonist
OCPB Reviewer	Bei Yu, PhD (For filing only)	Indication(s)	Moderate to severe dementia of the Alzheimer's type
OCPB Team Leader	Raman Baweja, PhD	Dosage Form	Extended-release capsules
		Dosing Regimen	QD
Date of Submission	08/20/2009	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/14/2010	Sponsor	Forest Laboratories, Inc.
PDUFA Due Date	6/21/2010	Priority Classification	Standard 10 months
7.1.1.2 Division Due Date	5/21/2010		

7.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
1. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				

Pharmacokinetics (e.g., Phase I) -				
7.2 *Healthy Volunteers-*				
single dose:				
multiple dose:	X	2	2	
7.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:	X	1	1	
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1	1	
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	2	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	

Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		7	7	
7.2.1.1.1.1				

7.2.1.1.1.2 Filability and QBR comments

7.2.1.2	"X" if yes	7.2.1.2.1.1.1.1 Comments
7.2.1.3 Application fileable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
7.2.1.4 Comments sent to firm ? 7.2.1.5		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		1. To evaluate the relative BA for 28-mg ER formulation (QD) compared to 10-mg IR formulation (reference product, BID) after single dose and at steady state. 2. To assess the effect of food on the 28 mg capsule ER formulation. 3. Request full detailed data for the "dose dumping with alcohol" experiment. 4. Inspection for MEM-PK-17 (BE between clinically used ER and to-be-marketed ER) is being requested. 5. Renal impairment labeling: switch ability from Namenda IR to Namenda [(b)(4)] for severely renally impaired patients.
Other comments or Information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUIXIA ZHANG
05/03/2010

YANING WANG
05/03/2010

HAO ZHU
05/03/2010

RAMAN K BAWEJA
05/03/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-525 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DNP		
Sponsor:	Forest Labs	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Namenda XR Extended Release Capsules	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Memantine Hydrochloride Extended Release Capsules	Date Assigned:	Sep 09, 2009
Indication:	Moderate to severe dementia of the Alzheimer'type.	Date of Review:	March 18, 2010
Formulation/strengths	Extended Release Capsules/ 7 mg, 14 mg, 24 mg, and 28 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission dates	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Aug 20, 2009; Jan 12, 2010; March 12, 2010	Aug 20, 2009; Jan 12, 2010; March 12, 2010	Sep 9, 2009	June 21, 2010
Type of Submission:	Original NDA		
Type of Consult:	IVIVC model/Dissolution method and specifications/waiver request for lower strengths		

23 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
04/05/2010

PATRICK J MARROUM
04/05/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-525 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DNP		
Sponsor:	Forest Labs	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Namenda XR Extended Release Capsules	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Memantine Hydrochloride Extended Release Capsules	Date Assigned:	Sep 09, 2009
Indication:	Moderate to severe dementia of the Alzheimer'type.	Date of Review:	Oct 8, 2009
Formulation/strengths	Extended Release Capsules/ 7 mg, 14 mg, 24 mg, and 28 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Aug 20, 2009	Aug 20, 2009	Sep 9, 2009	June 21, 2010
Type of Submission:	Original NDA		
Type of Consult:	IVIVC model/Dissolution method and specifications---FILING REVIEW		

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
10/21/2009

PATRICK J MARROUM
10/21/2009